MEDIDATA

Site Perspectives on Decentralized Clinical Trials

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Introduction

In the years before the global coronavirus pandemic took hold in 2020, clinical development strategies and trends were already shifting towards greater globalization, digitalization, and patient centricity. This shift, while slow, could be seen in multiple arenas: regulatory guidance advising on incorporating patient perspectives in trial endpoints such as the U.S. FDA's 2021 draft guidance on the use of patient-reported outcome measures (PROMs) in oncology trials; sponsors' initiatives on including more diverse patient populations; and rapid digitalization of business processes, enabling new approaches to trial conduct and patient engagement. The onset of the pandemic only accelerated the effects of these concurrent trends and factors, facilitated by technology.

Decentralized Clinical Trials (DCTs) saw a rapid uptick as patients were unable to travel to study sites due to travel restrictions and quarantines. This model of clinical trial design and conduct allows for certain activities (as specified in the clinical trial protocol) to take place away from traditional clinical research sites. It may come as a surprise to some that this model has existed for over twenty years, long before pandemic mitigation restrictions were put in place.

While DCT technologies have enabled patients and sites to participate in novel and innovative ways, there is a lack of qualitative and quantitative data on site perspectives on the use and implementation of these initiatives. To examine how this model has impacted site experiences, Medidata partnered with the Society for Clinical Research Sites (SCRS) to survey its members on a variety of DCT topics, including scope, perceived effectiveness, and enablement. Understanding clinical research sites' experiences and perspectives on DCTs will help industry stakeholders – from sponsors and clinical research organizations (CROs) to regulatory agencies – refine trial design, operational procedures, and regulatory policy to better serve patients and sites while optimizing outcomes for the global health community.

About the Survey Respondents

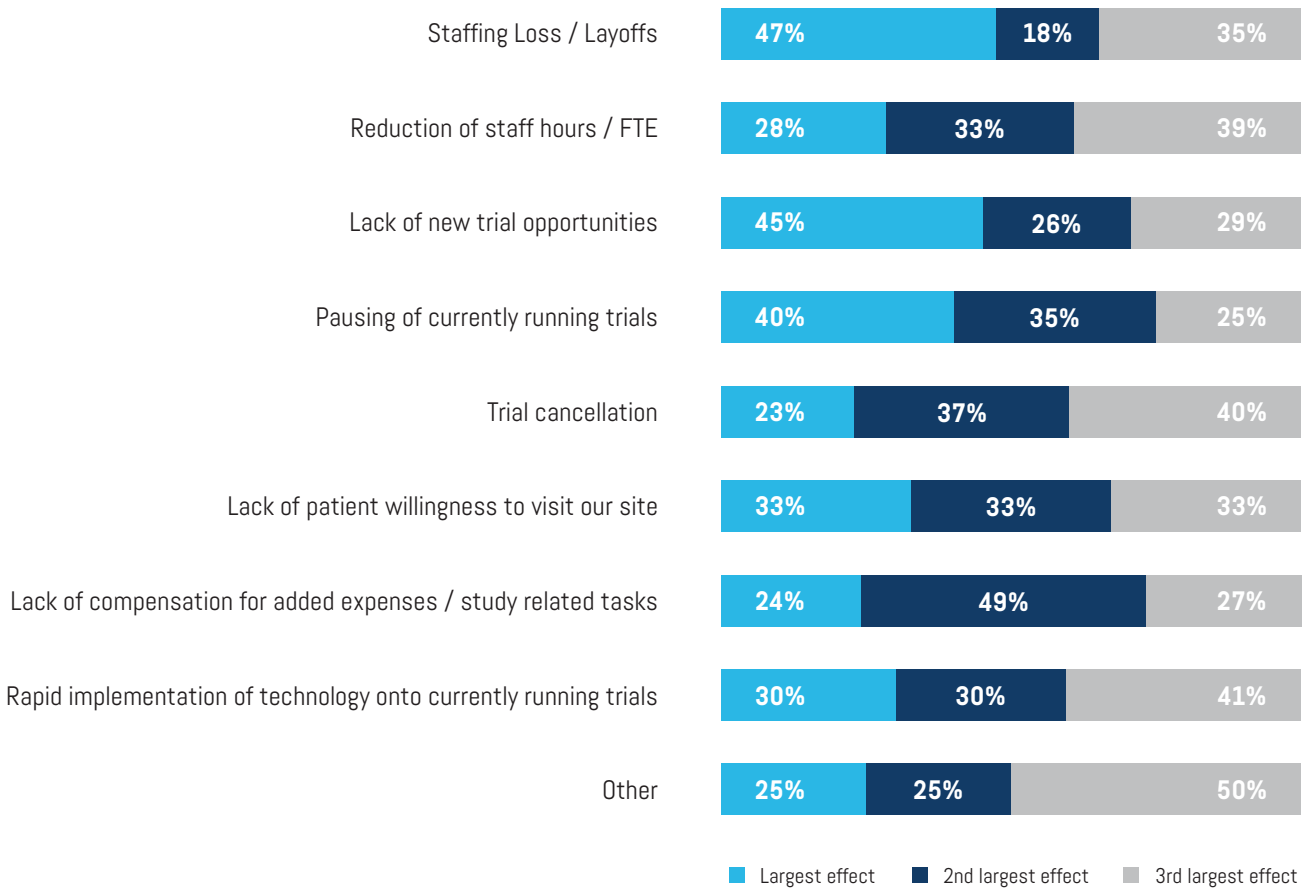
Conducted in early 2022, an online survey was sent to the entirety of SCRS's immediate and extended reach, including site directors and managers, study coordinators, and principal and sub-investigators, as well as site owners and business development personnel. Individuals who did not respond to the original invitation were provided with four additional reminder emails. A total of 135 sites participated, primarily representing geographically urban or suburban sites as well as some rural areas. Sites reported extensive therapeutic expertise, including endocrinology, cardiology, neurology, oncology, rare diseases, and ophthalmology.

Understanding the Impact of COVID-19 on Research Sites

To assess the impact of COVID-19 on research sites, respondents were asked to provide information on a number of operational and financial measures negatively impacted by the COVID-19 epidemic. Staffing losses (47%), a reduction in new study launches (45%), and delays/pauses of existing studies (40%) were reported as having the greatest effect.

The lack of compensation for added expenses (49%) incurred as a result of the pandemic, as well as trial cancellations (37%) and patient inability/unwillingness to travel to sites (33%), were reported as important secondary consequences negatively impacting sites. Please refer to Figure 1 for additional information.

Figure 1. In which of the following ways (choose the top three) was your site negatively affected by the pandemic/COVID related lockdowns?



Defining DCTs and Baseline Experience

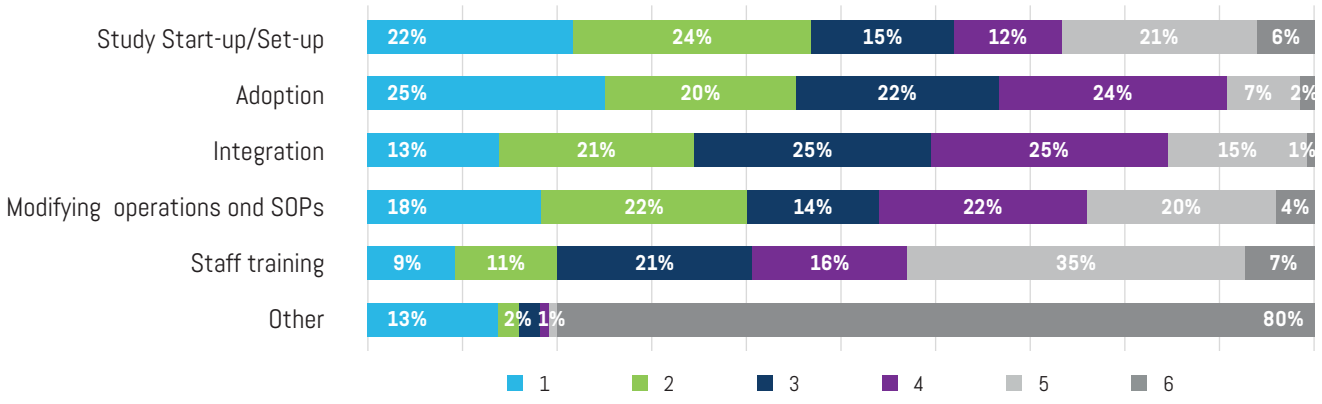
The FDA defines DCTs as a clinical investigation where some or all of the trial-related activities occur at a location separate from the investigator's location. Using technology, patients remotely engage in their trial activities, creating better patient experiences while enabling sponsors to execute faster, smarter trials driven by high-quality data, allowing for the utmost confidence in data collection and submission. Medidata DCT is an ecosystem of tools, people, and processes that allows patients, sites, and sponsors to participate, contribute, and monitor any clinical trial.

To understand if sites' definition of DCTs align with the FDA, respondents were asked to comment on their perception of a DCT. Survey participants offered a wide range of definitions. Some agreed with the definition offered, while others described the conduct or benefit of these trials, explaining that decentralized clinical trials "allow for visits to be completed at alternative locations," "take the burden off patients traveling to site," and enable "more remote visits, fewer on-site visits, [and] medications delivered to home."

Some respondents mentioned the tools or solutions that facilitate decentralized trial activities, including remote monitoring and study data collection, electronic diaries, and study visits completed at home via telemedicine, as well as tracking software to collect data on vital sign measurements. Another cohort of respondents expressed frustration with DCTs, saying that they entail "less interaction with patients," raise questions about safety or regulatory concerns, and result in more complications for sites.

These varied responses suggest that definitions of decentralized or hybrid clinical trials are ever evolving and dependent on one's role in clinical research, while also underscoring that a single, unified definition has yet to coalesce across the industry. What is clear from sites' perspectives is that decentralized clinical trials leverage technology to capture data and replace activities traditionally done at sites, but that they also require greater safety and adherence oversight, reduce site staff interactions with patients, and often add uncompensated work for sites.

Figure 2. Please rank the following challenges your site has faced as it pertains to the adoption of DCTs from most challenging to least challenging.



To understand what drives these perspectives, the survey asked respondents about their experiences and challenges with respect to conducting DCTs (Figure 2). Nearly two thirds of survey participants said they had participated in hybrid or decentralized trials, reporting that their top challenges in adopting this trial model included overall adoption and study startup activities. Integration, as well as modification of operations and standard operating procedures, ranked closely after that, suggesting that new technologies and processes introduced complications. However, despite such challenges, sites recognize the benefits that DCTs offer in terms of offering access to broader patient populations, as well as improvements to patient experience, diversity, and retention.

Of the 33% of sites who had not conducted hybrid or decentralized trials, most responded that they lacked the finances, patient population, staff, or technology required. Some suggested that they preferred and continued to see patients in person, or that they had concerns about oversight and regulatory or legal issues.

Evaluating Technology Enablement Tools

Next, regarding the technology solutions and infrastructure that facilitate remote trial conduct, the survey asked participants to report on their experiences with certain tools over the past two years and look ahead to their expectations for future usage. Solutions were grouped into eight categories: eCOA/ePRO, online/electronic recruitment, patient registries for pre- and post-trial engagement, electronic consent (eConsent), sensors and wearables, televisits, DCT/hybrid trials, and direct-to-patient drug/IMP shipments.

About 40% of sites participating in this survey reported that, in the past two years, they utilized electronic clinical outcome assessments (eCOA) solutions most of the time, while a little more than 20% said they did so half the time and 18% said never. In the next most-utilized category, electronic recruitment solutions, 51% said they employ this solution most or at least half of the time.

Interestingly, the data show that sites use many of these digital enablement solutions less than half of the time. More than 46% of respondents said they rarely used sensors/wearable technology or televisits in the past two years, and almost 50% said they have never used direct-to-patient drug or investigational medicinal product (IMP) shipments. The usage of eConsent solutions also skewed negative, with more than 60% saying they rarely or never used this type of system.

These data suggest that eCOA solutions are the most utilized DCT technology, with more than half saying they leveraged them all or most of the time. On the other side of the spectrum, direct-to-patient medication supply, sensors and wearables, and televisits were least utilized in the past two years.

Looking ahead, the data show that most sites expect to use more technology solutions in the next two years. More than 60% anticipate using eCOA most or all of the time, and 50% expect to utilize electronic patient registries at least half of the time, compared to 54% and 33% respectively over the past two years. Of those solutions with the largest deltas between past usage and expected future usage, more than 60% of sites report that they anticipate that televisits will play a role in at least half their trials, double that from the prior two years. There is also a marked increase in expected usage of eConsent, with nearly two thirds of respondents reporting that they expect to utilize eConsent half or most of the time, compared with the 31% who have used it in the past two years.

In the sensors and wearables category, three quarters of respondents reported they rarely or never used them in past trials. That number is reduced by half in future projects – more than 60% of sites surveyed expect these data capture solutions will be utilized in at least half of their trials. The data also suggest most sites expect to see more decentralized trials: only about 30% of sites said they conducted DCTs half of the time or more over the past couple years, compared to 55% who expect to run DCTs at least half the time over the next two years. Figures 3 and 4 below illustrate these trends and expectations.

Solution Focus: Direct-to-Patient Clinical Supply Delivery

Just over 46% of the sites participating in this survey reported that they have supported direct-to-patient (DtP) clinical supply delivery models via interactive response technology (IRT) or randomization and trial supply management (RTSM) software. Their experiences with DtP are nearly evenly divided between depot-to-patient and site-to-patient deliveries, with site-to-patient slightly more prevalent.

Nearly two thirds reported that communicating with the patient or depot is the most challenging aspect of supporting this solution, followed by difficulty with returns or supply accountability, difficulties sharing addresses, and discomfort with the lack of control they experienced during the process.

Comparing Past Experience With Future Expectations For Technology Utilization

Figure 3. Over the past two years, which of the following solutions or groups of solutions have you used within a clinical trial, and how often?

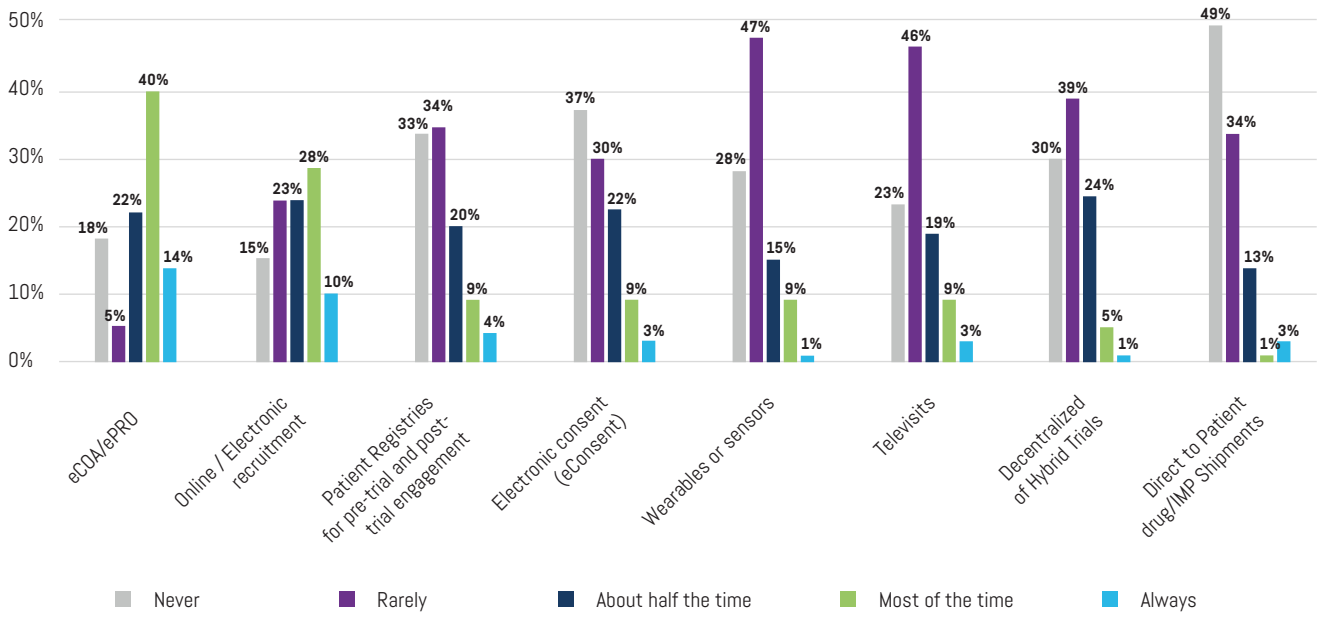
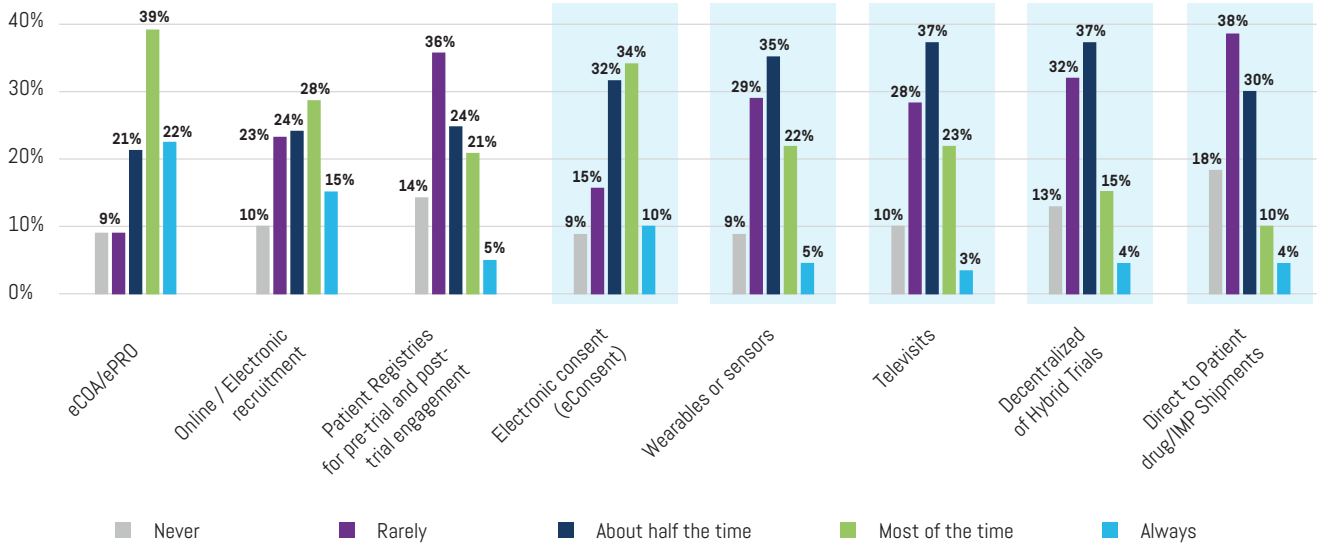


Figure 4. Thinking ahead to clinical trials over the next two years, how often do you anticipate using the following solutions?

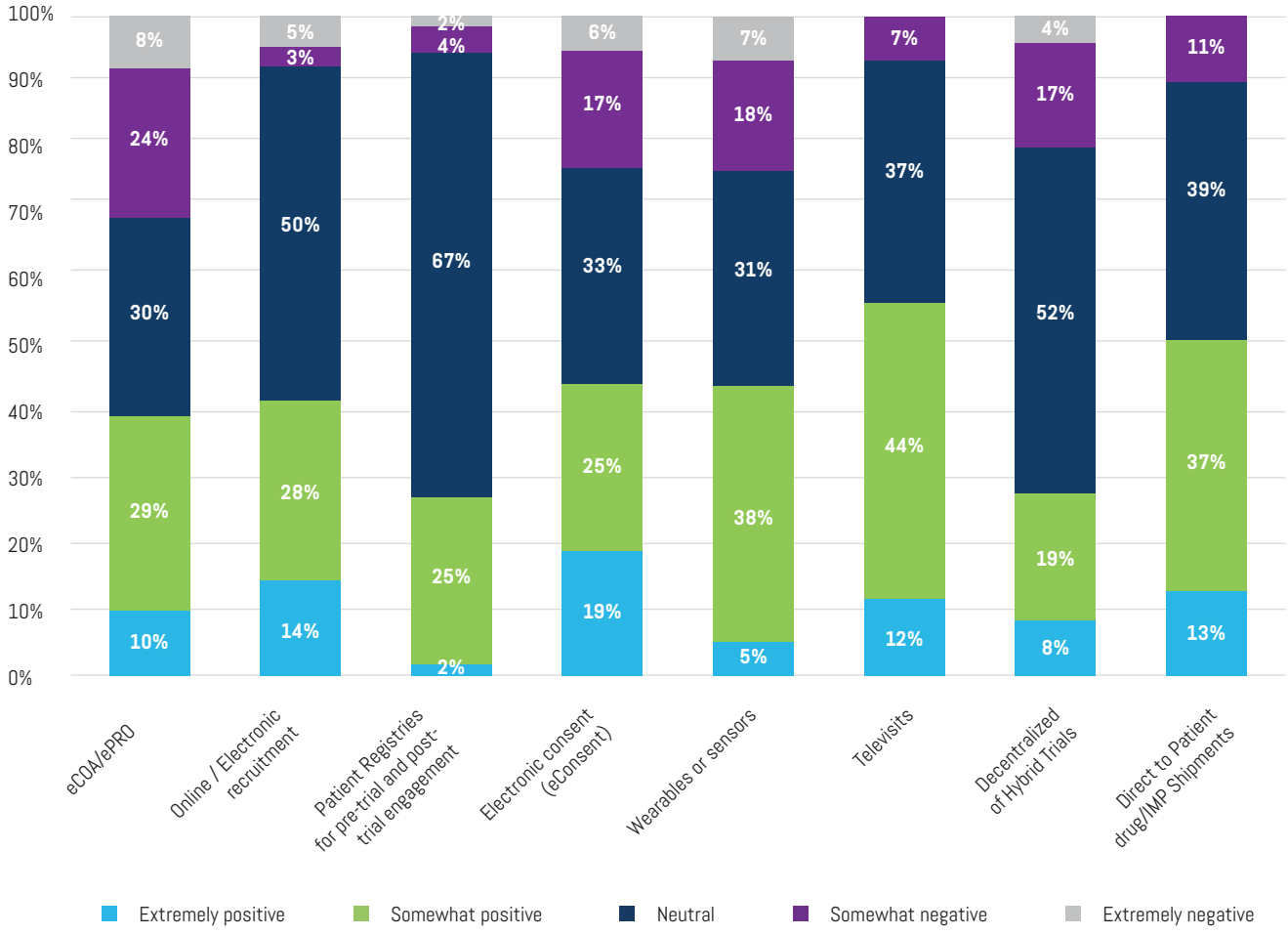


*Highlighted sections enforce comparison to previously collected data

User Experience

Building on this understanding of sites' technology usage, the survey asked participants to report on their satisfaction with these solutions or groups of solutions. More than 50% of sites reported a somewhat or extremely positive experience with eCOA, electronic recruitment solutions, patient registries, eConsent, televisits, and direct-to-patient supply solutions. However, 29% reported somewhat or extremely negative satisfaction levels with eCOA, and 30% said the same for eConsent and decentralized clinical trial solutions. Interestingly, most respondents reported positive, very positive, or neutral levels of satisfaction with all eight categories of solutions, suggesting these technologies do add value to clinical trial operations for sites.

Figure 5. Please rate your patients' experience using these solutions or groups of solutions



To gauge the impact of technology on clinical trial participants, the survey also asked sites to rate their patients' experiences with the same technologies. More than half of sites reported that televisits (56%) and DtP drug/IMP shipments (50%) were extremely or somewhat positive experiences for their patients, while decentralized or hybrid trials and patient registries (27% each) were the lowest rated under positive experiences. Of the responses for somewhat or extremely negative patient experiences, eCOA/ePRO (32%), wearables or sensors (25%), and eConsent (23%) had the worst ratings. A majority of sites (67%) thought patients had a neutral experience with patient registries, 15 percentage points higher than the next, decentralized or hybrid trials (52%).

The highest percentage of sites ranked electronic consent (19%), followed closely by online recruitment, direct-to-patient drug supply, and televisits solutions (14%, 13%, and 12% respectively), as extremely positive experiences for patients. Interestingly, eConsent (6%) was also a solution that sites rated as an extremely negative patient experience, as well as eCOA/ePRO (8%) and wearables or sensors (7%). No sites rated televisits or DtP drug/IMP shipments as an extremely negative experience for patients.

Site and patient satisfaction generally aligned with each other, although sites, on average, rated their positive experiences slightly higher than patients' experiences; however, this survey only targeted site staff, so patient satisfaction may be influenced by the sites' experiences and biases. The largest discrepancies between the site and patient experience ratings were for the following solutions: somewhat positive electronic recruitment experiences (site, 48%; patient, 28%); neutral electronic recruitment experiences (site, 14%; patient, 50%); neutral eConsent experiences (site, 13%; patient, 33%); and neutral DCT experiences (site, 33%; patient, 52%).

Subsequent questions about specific factors such as training, time and cost investments, and operational modifications may be helpful in deriving insights about these satisfaction ratings in future surveys.

Considerations and Factors Impacting Technology Adoption

With this clearer picture of sites' and patients' experiences, expectations, and satisfaction regarding digital enablement solutions, we can now look at the factors both driving and preventing technology adoption. Of the sites which currently use the aforementioned technologies, 18% cited staff workload and technology complexity as the top two factors limiting their utilization of eCOA solutions, while 15% cited training requirements as a top limiting factor (Table 1). For sensors and wearable technologies, the most significant factor is training requirements, followed by time and technology complexity.

Table 1. Based on the solutions you selected, what factors, if any, currently limit your usage of these solutions or groups of solutions?

Solution	Time	Cost	Staff workload	Need of additional staff	Upgrades to IT infra-structure	Trainer require-ments	Need for SOP or operational changes	Tool/Tech complexity	Nothing is limiting our use of this tool
eCOA/ePRO	12%	5%	**18%**	8%	6%	**15%**	5%	**18%**	13%
Online / Electronic recruitment	**14%**	10%	**17%**	8%	7%	10%	7%	7%	**19%**
Patient Registries for pre-trial and post-trial engagement	**18%**	11%	11%	**15%**	8%	9%	8%	7%	**13%**
Electronic consent (eConsent)	13%	4%	10%	2%	12%	**14%**	13%	**16%**	**17%**
Wearables or sensors	**14%**	8%	13%	7%	8%	**19%**	4%	**14%**	13%
Televisits	7%	7%	**13%**	7%	**14%**	12%	12%	8%	**19%**
Decentralized of Hybrid Trials	9%	10%	12%	10%	8%	**15%**	**15%**	8%	**12%**
Direct to Patient drug/IMP Shipments	11%	5%	**16%**	6%	2%	14%	**20%**	8%	**19%**

In terms of future utilization, a significant cohort of respondents said staff workload and time are the primary impediments to employing electronic patient registries, while infrastructure upgrades and revisions to standard operating procedures are noted as the top two limiting factors for the usage of televisits (Table 2).

Notably, "nothing is limiting our use of this tool" was cited as a top-tier response for both current and expected solution utilization. Although sites have reported in this survey and others that decentralized clinical trials result in additional uncompensated costs and significant changes in process, they only marked "cost" as one of the top impediments in one instance for both current and future technology adoption. This suggests that the benefits of technology and of decentralized clinical trials, in general, outweigh the costs, and it provides insight for sponsors and clinical research organizations who may be looking for specific ways they can support sites conducting hybrid or decentralized trials. Some sites responded that they would prefer their own in-house solutions over a sponsor's, CRO's, or third-party vendor's solutions; this response may prompt dialogues among stakeholders about investing in, implementing, and managing technology infrastructure that fulfills their sites' needs.

Table 2. For the solutions or groups of solutions, you do NOT currently use, what factors, if any, would limit your usage of these solutions in the future?

Solution	Time	Cost	Staff workload	Need of additional staff	Upgrades to IT infra-structure	Trainer require-ments	Need for SOP or operational changes	Tool/Tech complexity	Nothing is limiting our use of this tool
eCOA/ePRO	**13%**	**19%**	**13%**	**13%**	6%	6%	6%	6%	**19%**
Online / Electronic recruitment	0%	6%	**17%**	**17%**	**17%**	11%	11%	0%	**22%**
Patient Registries for pre-trial and post-trial engagement	**18%**	8%	**28%**	**15%**	5%	5%	5%	3%	**15%**
Electronic consent (eConsent)	7%	7%	10%	0%	10%	**12%**	**20%**	**12%**	**22%**
Wearables or sensors	3%	7%	3%	3%	**14%**	**17%**	7%	10%	**34%**
Televisits	0%	0%	4%	0%	**27%**	**19%**	**27%**	15%	8%
Decentralized of Hybrid Trials	5%	8%	8%	18%	8%	**13%**	**21%**	8%	**13%**
Direct to Patient drug/IMP Shipments	4%	4%	9%	4%	6%	**20%**	**24%**	6%	**24%**

Other DCT Technology: Remote Monitoring Solutions for Source Data Verification and Reviews

Another technology solution that enables remote trial conduct, off-site clinical trial monitoring systems, are increasingly utilized to enable remote source data verification (SDV) and source data review (SDR). More than half of sites believe this technology to be a viable solution for data quality and patient safety oversight. Of the 43% interviewed in this survey who do not currently use this solution, most said it is because sites are not compensated for the additional activity and costs associated with it. They also reported that the lack of integration between EHR, EMR, imaging, and EDC systems makes this solution impractical for SDV/SDR. Others suggested that their technology or processes are not prepared to support remote monitoring for SDV/SDR or described concerns about increased risks, complications, and reduced communication among stakeholders.

Sites that utilize remote monitoring solutions for SDV and SDR reported that it facilitates efficient engagement with clinical research associates (CRAs), reduces inspection findings, and helps remediate issues cited in inspection findings.

The most challenging aspects of utilizing remote monitoring for source data verification and reviews are related to document management (e.g., scanning, uploading, or exporting documents), lack of integration between systems, and managing CRA access to EHR/EMR systems.

Reflections About the Current State of Clinical Trials

To conclude the survey, respondents were asked what they would change about clinical trials. This broad and open-ended question yielded important insights into the current state of clinical research from the point of view of one of its most critical constituents and revealed recommendations for industry. Key responses are summarized below:

1. Workloads and administrative burdens on sites have increased considerably. Trials may utilize many disconnected portals and apps, each requiring its own training, login, and SOPs.

2. Sites are not compensated adequately or fairly for additional time, cost, and other burdens.

3. Clinical trials today are reducing patient-physician interactions. The on-site visits and personal connection with patients, as well as with their spouses, families, and caregivers, are critical to their participation and the trial's success.

4. More qualification, training, and support is needed for clinical research associates.

5. Sites would prefer to have insight or input into vendor selection. It impacts the participation experience for sites and patients, as well as the regulatory review process.

6. Patients incur uncompensated costs in terms of time and convenience when utilizing telehealth and other solutions.

7. Engaging sites before and during protocol design could make trials more realistic (e.g., larger windows for assessments, assessments placed in an order that makes sense in practice, more flexibility for patient visits, and less PKs when possible).

8. Changing and increasing regulatory requirements reduce efficiency and increase site burdens.

Applying Lessons Learned

It is well-established that the decentralized clinical trial model enables greater patient participation and diversity, increases the quantity and quality of data in support of trial endpoints, and enhances other aspects of clinical trials. As the linchpin between sponsors, CROs, patients, and vendors, sites remain critical partners on the front lines of clinical research. Utilization of DCTs will inevitably grow, and it is essential to measure the effectiveness of strategies and technologies underpinning DCTs, not only to understand the effectiveness of solutions as well as areas for improvement, but also to establish metrics to evaluate against future data.

The results of this survey provide important metrics to encourage open dialogue and ongoing feedback, so that industry stakeholders can continue to learn and respond by making meaningful adjustments that ease the burdens of trial participation. Empowering sites by identifying these pain points and minimizing challenges will extend the reach and impact of clinical research, ultimately providing patients, sites, and sponsors with better clinical trial experiences.

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