MEDTECH**DIVE**

From Bench to Bedside:

Evolving Clinical Trial Designs, Protocols and Technology Strategies
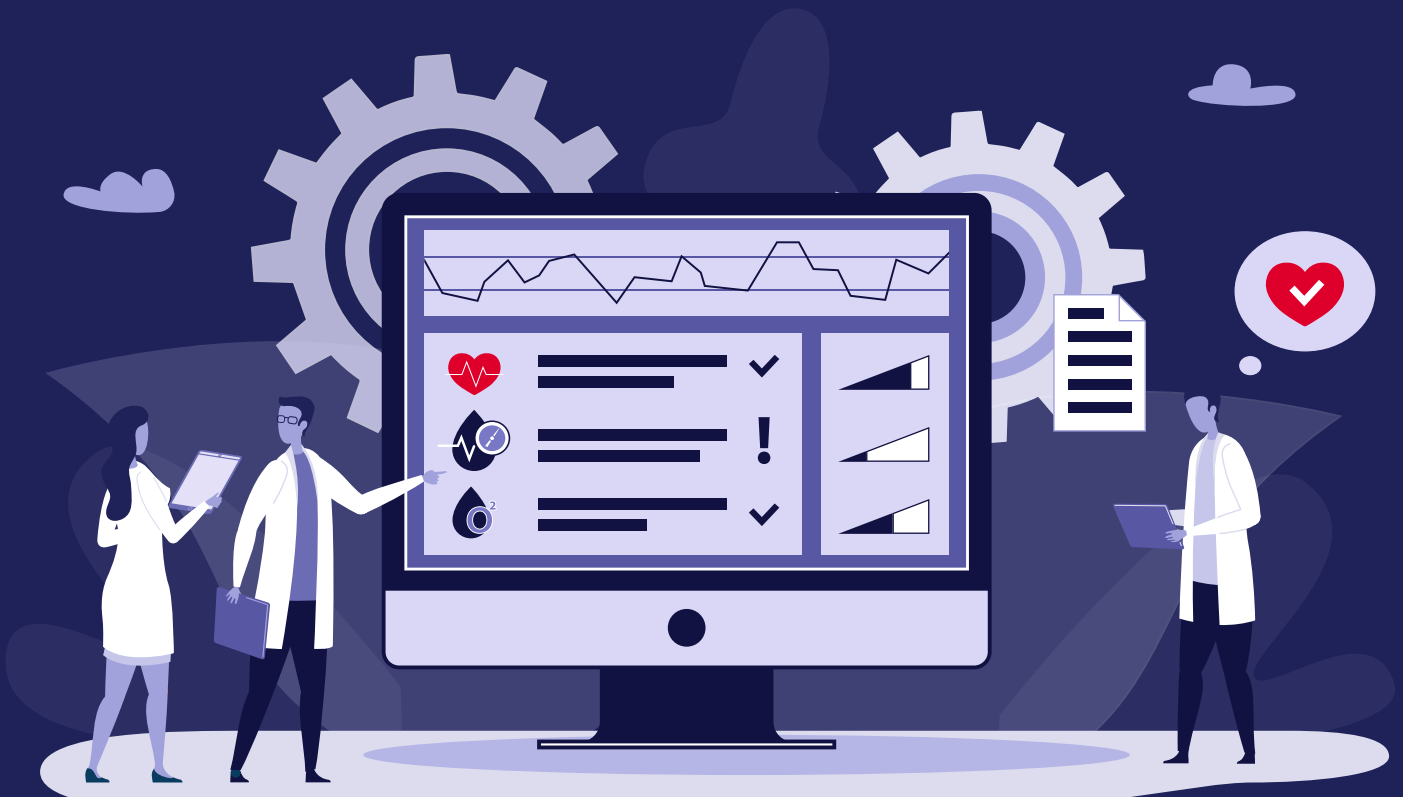

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Introduction

In many ways, the COVID-19 pandemic served as an accelerator for innovation in biomedical research. Of course, the pandemic also revealed many of the shortcomings in the clinical trial landscape: Studies were halted, failed to enroll patients or experienced very low follow-up rates when the public health emergency restricted in-person site visits. But, on the upside, the pandemic drove the adoption of new trial designs and protocols, invited greater patient-centricity and increased reliance on digital technologies.

The popularity of decentralized clinical trials (DCTs), for instance, skyrocketed in 2020. Sponsors and contract research organizations (CROs) raced to adapt protocols to accommodate social distancing and a near-total moratorium on non-essential medical visits. In response, the FDA provided new guidance, loosening review and approval processes.[1] Many sites, sponsors and CROs implemented new digital tools on the fly, sometimes without giving a great deal of thought to longer-term data capture and technological transformation strategies.

Now that the peak pandemic period has receded and in-person site visits are back, some stakeholders are questioning the value of the investments they made under duress. And the industry remains ripe for disruption: Treatments are unaffordable for many patients, in large part because of the high costs and failure rates associated with drug development. Sponsors struggle to recruit trial participants whose diversity mirrors that of the general patient population. Process inefficiencies abound. Much work remains to be done if the full potential of medical and scientific research is to be realized in the clinic—and reflected in real-world patient outcomes.

Emerging innovations in clinical trial design and execution promise to help biopharmaceutical and medical device companies overcome some of these challenges. Novel trial types and protocol designs may accelerate research progress. They also may increase the probability of a therapeutic's approval and improve participant experience. But they are inherently more complex than conventional randomized controlled trials (RCTs): They demand more sophisticated data capture, management and interoperability capabilities than have been standard so far.

This report takes a closer look at these promising innovations and highlights some of the signals regulators are sending. And it offers advice from industry experts on steps that medical device and pharmaceutical companies can take today to prepare themselves for the future of clinical trials.

The Coming Revolution in Clinical Research

As has been the case for many years, drug and device development today is both expensive and failure-prone. On average, if the costs of failed trials are included in the total, the median research and development cost of each new therapeutic that reaches the clinic is $1.1 billion.[2] A recently approved treatment for Alzheimer's disease that slowed the rate of cognitive decline in clinical trial participants will cost patients over $26,000 per year, with Medicare participants expected to pay more than $5,000 out of pocket.[3] New—and potentially lifesaving—cancer treatments are even more expensive, with the costs of cell and gene therapies such as CAR-T mounting well above six figures.[4]

The discovery process is also time-consuming and risky. More than 90 percent of promising candidates that enter development pipelines never make it all the way through the process.[5] For those that do, rapid approval is far from guaranteed. The FDA approved only 37 drugs in 2022, far short of its recent historical norm of 51 approvals per year. In fact, this was the lowest number of FDA approvals in any year since 2016.[6]

While presiding over an agency that has curtailed approvals, the recently reinstated FDA Commissioner Robert Califf continues to emphasize the importance of speeding and streamlining the approval process. At the Drug Information Association's most recent annual meeting, he spoke about the importance of "fast failure."

"Both successes and failures can be critical to guiding developers to the best and most efficient pathway," Califf said. "This can help them save time and money, prevent wasted or duplicative efforts and ensure speedy development of the best and most effective products."

Industry experts have interpreted the approval slowdown as a temporary stage in which the FDA will ramp up its use of technologies to evaluate the data captured in trials. To be ready for this increased scrutiny, sponsors need to present clean, high-quality data in sharable formats. To rein in development costs, they need to accomplish this efficiently. And to recruit adequate numbers of diverse participants in a world where this is becoming increasingly difficult, they need to improve participants' experience and reduce the burden of taking part in trials.

Medical device and pharmaceutical companies also must embrace innovations in trial design. This is a must if they intend to overcome inefficiencies that have impeded profitability, slowed approvals and made the discovery and development of new therapeutics such a risky process.

Innovative clinical trial designs and protocols

Sponsors share important objectives: to mitigate the risks involved in drug development, streamline evidence generation, improve recruitment, increase participants' diversity and boost participant experience. To realize these, they have to be willing to experiment with trial types and protocols. Innovations they will likely experiment with include:

- **Decentralized clinical trials:** DCTs are not truly new. Sponsors and sites have been performing clinical trials at a site other than the traditional site for more than a decade.[7] However, DCTs gained real momentum when the pandemic forced their use. Sponsors and CROs have since discovered that many participants prefer DCTs because of their convenience, making retention easier. In addition, DCTs that leverage digital health technologies can capture greater volumes of highly accurate data than on-site RCTs, making additional endpoints or more robust findings possible.

- **Adaptive protocols:** It's becoming more common for investigators to use evidence generated over the course of the study to modify subsequent study activity. This flexibility allows researchers to learn as they go and improve safety and efficacy assessments and interventions.

- **Blended-phase trials:** Increasing numbers of studies are beginning to consider factors traditionally assessed during phase 2 or even phase 3 during phase 1. The goal is to "fail faster" and streamline later-phase investigations.

- **Synthetic control arms:** The FDA has been signaling its growing commitment to using real-world data in decision-making.[8] This opens the door for sponsors to take advantage of health care data sourced from routine patient care—including electronic health record (EHR) and administrative claims data—in place of data collected from study patients enrolled in a control arm. Synthetic control arms are proving especially valuable in rare disease research and for investigating treatments when the patient's prognosis is poor or few alternatives are available.

- **Basket and umbrella trials:** In these nontraditional trial designs, a single intervention is tested for efficacy against multiple indications (basket trials) or multiple interventions are tested within a single trial for one intervention (umbrella trials). Both allow for more flexibility in pairing patients with therapies—and more efficiency in determining efficacy—than would be possible in a standard RCT.

- **N-of-1 trials:** Increasingly personalized trial designs allow for interventions to be tailored to the individual disease state and genetics of each patient. This makes it possible to develop treatments for very rare diseases that would have been extremely difficult to bring to market in the past.

New kinds of studies that better match the needs of precision medicine will prevail in the future of clinical trials. Increasingly, protocols will be designed to identify patient-specific drug activities—as well as to meet the patients' expressed needs and attract diverse participants. This will require taking patient—and clinicians'—perspectives into consideration from the earliest stages of trial design. It will require greater agility and flexibility on the part of sites, sponsors and CROs. And it will require investments in technologies that can support this agility, flexibility and responsiveness.

What all of these novel trial types and protocols have in common is greater complexity than is typical of traditional RCTs. To succeed in tomorrow's clinical research landscape, stakeholders will need to use tools that help them manage this increased complexity. They'll need to make advances in data management, use artificial intelligence (AI) and machine learning (ML) to create efficiencies, and adopt big data analytics to derive insights from their data. The more innovative and complex trials become, the more closely their success will be tied to the right digital technologies.

"Let's take oncology as an example," says Nicole Latimer, Chief Executive Officer at Medrio. "It used to be that pharmaceutical companies were looking for drugs to treat cancer. Then, they wanted to treat breast cancer. Now, they're doing studies that target HER2-positive breast cancer with LSP1 genes. This means the number of people who might be eligible to take part in any given trial keeps shrinking."

"At the same time, it's becoming more and more complex to figure out whether or not a treatment is effective. The only way to resolve this apparent paradox is by applying technology. Today's sponsors need to be able to build a technology platform that's standardized enough to support their entire science platform, that's scalable and that's built upon templates that make it simple to configure, change and adapt protocols as they go along."

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Chief Executive Officer,
Medrio

Regulatory Shifts: The Push for Decentralization, eConsent and Digital Health Technology Adoption

Since the start of the pandemic, regulators including the FDA and the European Medicines Agency (EMA) have signaled and issued new guidance on the use of digital technologies in trials, encouraging sponsors to innovate to increase efficiencies, improve participant experience and promote diversity. Many of these efforts are reactive—with regulatory bodies struggling to keep up with the accelerating progress of technological innovation—but the intent is to encourage progress.

Signs are clear that regulators will continue to encourage (or mandate) increased efficiency, greater patient-centricity and growing reliance on eSourced evidence in clinical research. Regulators are also issuing statements on the ethics and governance of AI in health care and biopharmaceutical research.

Relevant statements include the following:

- In June 2021, **the World Health Organization (WHO) issued new guidance on the ethical use of AI in health care**, including in health research and drug development.[9] The guidance supports improvements in the quality of data used for public health and regulatory decision-making, as well as the application of AI to expedite drug development and make it less expensive and more effective. **The FDA recently published a discussion paper and request for feedback** on the use of AI in the development of drugs and biological products.[10] Like the WHO, the FDA is encouraging the responsible use of AI, and it's inviting conversation about the creation of principles, standards and best practices to govern AI/ML in drug development applications.

- **The FDA released its long-awaited first draft guidance on decentralized trials.**[11] It also continues to encourage the use of digital health technologies for remote data acquisition (as outlined in its 2021 guidance on the topic).[12] The intention here is to use technology in a way that enables trials to include remote elements while continuing to meet the same investigational requirements that are mandatory for traditional site-based clinical trials. The final version of this guidance, expected in December 2023, likely will enable sites and sponsors to leverage data collected through health care integration and centralized pathways to streamline protocol designs.

- **New guidance from the ICH** emphasizes that investigators should limit the amount of data collected in trials to information that will be shared with regulatory bodies for assessment purposes, or that can be assessed in accordance with the protocol's endpoints.[13] The goal is to minimize complexity and reduce the costs and risks associated with storing excessive amounts of data.

- **The FDA has also issued draft guidance on improving participant diversity** in clinical trials.[14] This guidance aims to ensure that populations that are frequently underrepresented in biomedical research—despite tending to bear a disproportionate disease burden—can be included in studies in ways that ensure that findings truly represent the populations that will be using the drugs.

- The FDA created a **Digital Health Center of Excellence** in 2020.[15] Intended to coordinate digital health work across the entire agency, DHCoE will promote digital health innovation through several key strategies. One is to encourage the creation of industry partnerships to connect digital stakeholders.

Accelerating Progress: How the Industry Can Ready Itself for the Future of Clinical Research

Patient-centricity is coming to the fore across all areas of health care, and biopharmaceutical research is no exception. Regulators are signaling their intent to increase trials' accessibility, which will make it easier to recruit participants who reflect patient populations for whom the therapeutic is intended.

Decentralized trials make it easier to include participants who would otherwise be left out for a variety of reasons. They may live too far from trial sites or in health care deserts. They may lack transportation or be unable to get time off from work to visit trial sites. They may live in communities where few people (including health care providers) are aware of current clinical research. Reducing the burden associated with traveling to a central clinical trial site by decreasing the number of required site visits tends to inherently increase participant diversity.

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"To truly increase access, you need to align trial designs to fit both patients' needs and their will."

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Program Director at the Decentralized Trials and Research Alliance, Chair of the Strategic Advisory Board at Curebase, and Founder and Owner of jemTech LLC

But simply adopting DCTs is not enough, says Jane Myles, program director at the Decentralized Trials and Research Alliance, chair of the Strategic Advisory Board at Curebase, and founder and owner of jemTech LLC. "To truly increase access, you need to align trial designs to fit both patients' needs and their will," she explains. "This means aligning protocols to what participants want, both by asking patients for input when writing protocols and by ensuring that included elements like wearables or other digital tools are well supported and easy to use. As an industry, we're not there yet, but regulators are sending many signals to remind us that this is where we need to go."

Although DCT activity is forecast to increase throughout 2023 after a slowdown in 2022, only a minority of today's trials include decentralized elements. The most common clinical trial component to be decentralized is digital data collection, with remote monitoring using sensors, devices and trackers also growing in popularity.[16] To overcome the current inertia, sponsors will need to adopt technologies that ease and streamline the process of data collection as well as trial management, randomization and supply chain management.

Several factors will likely spur sponsors to make these technology investments. Chief among them is pressure from regulators.

"Over the past couple of years, the FDA has been pushing harder and harder for participant diversity so that therapies can be tested on populations that are truly representative," says Dr. Daniel Fox, founder and CEO of the Clinical Research Payment Network. "Diversity plans will have to be established and approved within every protocol by 2025. And the more diversity requirements there are for protocols, the greater the n-value your study will require to obtain statistically valid results. I think that decentralization mandates will ultimately push decentralized trials and health care integration into the forefront of the clinical research landscape, because these will be the only ways that sponsors can capture the data that they'll need."

It's likely that financial pressures will drive technology adoption as well, since the need to create efficiencies will become more pressing as discovery and development costs continue to climb. Regulatory pressure may come to bear in this arena as well, since legislators continue to push for health care affordability.

"Imagine a world in which treatments are truly personalized, in which there's one medicine per patient," says Latimer. "One problem that will arise—if the industry can't create new efficiencies—is that we'll then have $1 billion in drug development costs per patient. If regulators are successful at exerting downward pressure on prices, it's likely that we'll see major pharmaceuticals thinking carefully about how to create efficiencies in the development process. This will include the adoption of technology, as well as the creation of standards that allow for data exchange."

What's Needed for Success

For sponsors to adopt the technology platforms that will make possible tomorrow's innovative protocols and more accessible and inclusive trials, they'll need to take several steps.

- **Design trials with digitization in mind from the start.** One reason DCT adoption in 2020 wasn't wholly successful is that protocols weren't created to work with digital tools, data flows and processes. Instead, analog and paper-based processes were adapted for remote use. This is quite different from designing trials to take full advantage of digital protocols and digitized processes.

  "It's analogous to operating with entirely digitized data flows—instead of using PDFs and Word documents, which are really just digital versions of paper documents. Digitized data flows change how you collect, process, analyze and output the results of trials," Myles says.

- **Focus on standardization.** It might seem counterintuitive, but personalizing medicine demands standardizing technology. Leveraging templates to collect data across multiple studies makes it easier to launch new trials, made mid-study adjustments and do cross-study analysis.

  "I'd say that 80 percent of a pharmaceutical or medical device company's clinical trial technology platform should be completely standardized," says Latimer. "By building out data fields and metrics that are consistent across studies, stakeholders will save time, create efficiencies and make it easier to be flexible."

- **Pay attention to change management— which goes broader and deeper than technology implementation.** Stakeholders in biopharmaceutical research today often hold onto paper-based processes because their standard operating procedures are associated with these processes. Often, trials are under tremendous time pressure, and creating new SOPs can lead to short-term delays. These will be worthwhile if the result is future trials that are massively expedited, but sponsors need to think long term and consider the human elements involved in creating change.

- **Strive for interoperability.** While universal standards enabling data exchange are not yet a reality in the pharmaceutical sector, there's hope that they may come soon. This will make it easier for sites to work with multiple sponsors and CROs while using highly efficient processes. It will also enable EHR data to be used more widely in pre- and post-market research, including for comparators.

  "Creating data standards will go a long way towards creating efficiency in this industry because it will provide a language that everyone can understand," says Dr. Fox. "This will allow for greater collaboration, making it possible to build new alliances across ecosystems."

- **Work to broaden patient, clinician and community involvement in research.** By increasing the diversity of physicians who participate in clinical trials—whether as investigators or in other roles, even without being on the trial team—it's possible to increase the diversity of the patient populations you reach. When sponsors encourage patient self-registration and work with patient advocacy groups, they can reach much larger groups of people suffering from rare diseases than would otherwise be possible. By asking for—and listening to—patient input early in the protocol design process, stakeholders can create trials that address real-world needs and are truly patient-centric.

- **Move away from paper.** Paper-based processes in clinical research are inherently inefficient, since data must be recorded once (on paper) and then manually entered into digital systems. Legibility issues abound, making them error-prone. They require additional source data verification and monitoring. All of these inefficiencies can be eliminated through the use of electronic data capture.

Realizing tomorrow's efficiencies today: the power of AI

Among the most rapidly evolving subfields in technology, artificial intelligence has captured the public imagination. Even as regulators continue to debate the ethics and risks associated with its use, industry leaders are racing to implement AI to comb through large volumes of data, monitor in-process trials for errors and anomalies, and identify significant findings in historical trial results.

AI can handle big-data problems that are difficult for humans to address, so it's well-suited to analyze the enormous amounts of data that sensors and wearables can generate. It also is able to search large databases to find good matches for trial participants; these matches can be part of synthetic control arms in trials. Investigators can use AI to refine clinical trials by analyzing past trials for factors that were useful—or data types that actually didn't need to be collected. And large language models can even be used to draft trial protocols, assessment schedules and consent forms. Ultimately, AI promises to create new efficiencies, enhance data quality and improve the participant experience—with potential benefits for medical device and pharmaceutical companies, health care providers and patients alike.

What to Look for in a Future-Focused Technology Solution

While there's widespread agreement about the importance of moving away from paper-based processes in clinical research, it can be more difficult to figure out where to start digitizing, or which aspects of trials should be prioritized for tech-driven innovation.

Focusing on just a few factors when evaluating eClinical technology can help stakeholders make investments that will actually simplify processes that continue to grow more complex. In particular, look for technologies that offer:

- **Ease of use.** Biomedical research is inherently a complex endeavor. Configuring your technology setup doesn't have to be. The best clinical technology tools make life easier for both clinical researchers and trial participants.

- **Flexibility.** eClinical technology that leverages templates so that you can easily make mid-study changes—with no need to take trials down or introduce costly delays—is a must-have in an increasingly agile world.

- **Interoperability.** API-driven data exchange makes it possible for stakeholders across the research landscape—including partners, vendors and other third parties—to share the same knowledge base and find the right information in one place. Interoperability will make it easier for sites to manage multiple trials at the same time, and for investigators to take advantage of others' research and existing health care data to advance the frontiers of science.

- **The ability to capture data offline.** This means home health care workers or visiting nurses can use the tools even in places where connectivity isn't available.

Conclusion

The pandemic taught us the importance of flexibility and agility, but it also showed pharmaceutical leaders how difficult it can be to create lasting change in a world where it's easy to stick with existing paper-based processes. This isn't a future-focused strategy, though. As innovations like precision medicine and AI-designed clinical trials move from the cutting edge to the everyday, clinical research will not be successful if its processes are stuck in the past. And the industry will not be able to meet regulators' increasingly stringent calls for diversity, cost-effectiveness and efficiency in clinical research.

Adopting new digital-first procedures, designing protocols to take full advantage of technology's capabilities and leaning on AI to create manifold efficiencies won't just be beneficial in the months and years to come. Industry leaders won't be able to survive without it.

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