White Paper

Delivering clinical trial continuity during COVID-19

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Executive summary

We have entered a new era of clinical development. In response to COVID-19, the industry took a great leap forward to bring clinical trials closer to patients – most of whom had to stay at home – and at a scale never achieved before. Site access constraints and elevated concerns about patient safety in the pandemic environment sparked regulatory agencies to expand their guidance to include the use of virtual clinical trial tools – from remote monitoring to telemedicine, direct-to-patient shipment of investigational medicines to the use of home health nurses in clinical research. Many sponsors and clinical research organizations embraced this opportunity to innovate and use this newfound urgency to utilize innovative, flexible clinical trials models and approaches to ensure critical drug development continued through the pandemic.

Through this experience, as drug developers more readily adopted remote, patient-centric tools to keep patients safe and studies progressing, technology-enabled clinical trials solutions, including virtual trial models and remote clinical monitoring, are providing a much-needed lifeline to trial continuity and priming the drug development ecosystem for greater adoption of patient-centric clinical trials in the future.

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The global pandemic has added complexity to the already nuanced clinical development landscape, making innovation within clinical research critical to advancing human health. Looking ahead over the coming months and years, we expect the demand for innovative clinical trial models, technologies and approaches to expand at a pace like never before. While patient access has been limited during the pandemic, ongoing issues facing clinical development require new patient-centric innovation and faster pathways imperatives going forward.

Perhaps our industry's greatest opportunity to ensure critical clinical development continues through the pandemic and beyond is to rethink how trials are designed and executed. Since the first clinical trial in 1949, research has been logistically centered within a (or many) site(s) – often a large, well-funded medical facility in a populated area. Not much has changed in the decades that have followed. But today, we have a chance to redefine not only what a research site needs to look like or how it operates, but also how patients engage in that research.

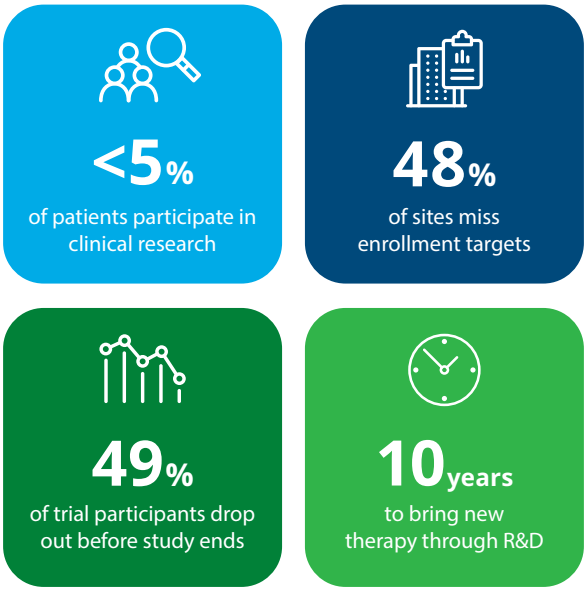
During the COVID-19 pandemic, we've seen a shift in how trials are designed and executed. In some cases, in-flight studies following traditional research models have shifted to hybrid formats, where a portion of site-based visits remain while other components of the trial are coordinated with patients from their home. Others have made the leap into a fully decentralized model where all study components are completed outside of the site.

There are many factors that play a role in how trial adjustments are implemented. This paper will discuss how clinical trial models are evolving as sponsors rethink the traditional research paradigm and adopt patient-centric clinical technologies and approaches, including telemedicine and remote clinical monitoring. With COVID-19 giving urgency to this transformation, the scope of this discussion will focus on two priority areas for sponsors and researchers alike: better understanding the need for potential shifts to decentralized trial models and what sponsors need to consider as well as a deeper look into key components of virtual trials.

Shifting from traditional approaches

When planning and conducting traditional clinical trials, challenges that end up costing time and money are almost inevitable. Site-based approaches can create expensive obstacles for investigators, patients, and drug developers. But, even more importantly, in some cases, these challenges can affect whether a trial or study is completed as planned, to reach the submission milestone.

Efficient patient recruitment and engagement has eluded clinical research for decades, costing sponsors time and money. Less than five percent of patients participate in clinical research. The reasons are numerous – and sometimes very personal for a patient and their caregivers – but some commonly cited reasons include geographic proximity of patients' homes to research sites, the number of site visits and the amount of time required to participate in a trial.



Of those who do enroll in a study, nearly half drop out before their study ends.

As COVID-19 sparked widespread site closures and travel bans, the logistical challenges of site-based trials were amplified. Patients, Clinical Research Associates (CRAs), and site personnel could no longer connect face-to-face. The future of clinical trials was jeopardized as patients were unable to complete study visits, receive scheduled dosing, or participate in necessary on-site screenings. Site staff were unable access study records, collect patient lab draws or conduct patient interviews, and site and data monitoring became limited.

Ideally, decentralized clinical trials approaches are selected and integrated into a clinical protocol during the study design phase long before recruiting begins. In the midst of the COVID-19 crisis, sponsors were pushed to consider alternative patient-centric, rather than site-centric, approaches to ensure trial continuity.

REGULATORY GUIDANCE EVOLVES

Swift, responsive regulatory action was a critical catalyst to adapting trial protocols and workflows to continue research during this global pandemic. Regulators across the global quickly acknowledged the need for operational flexibility. Varying regulatory guidance encouraged sponsors to complete risk assessment, employ risk mitigation measures, and consider integrating virtual elements into clinical trials already in progress to address urgent patient safety issues and minimize disruption for study participants, sites, and data collection. Even those who previously did not support virtual trial elements are now allowed their limited use.

The rapid support from regional agencies for virtual tools and models during the pandemic is a valid indication that regulators see patient-centric technologies and approaches as viable solutions to this global crisis and potentially beyond. For now, the ongoing uncertainty related to COVID-19 means regulatory guidance and opinions will continue to evolve, offering sponsors resources that inform their decisions around regional resource allocation, efficient shipment of study drug and supplies, and safety monitoring.

TRIAL CONSIDERATIONS

Some sponsors and sites are still uncertain of how to shift trials to hybrid or virtual models and using remote monitoring while ensuring compliance, continuity, and patient safety. As there is no one-size-fits-all approach to trial design and execution, sponsors need to consider multiple factors at the individual trial level when tailoring adjustments for COVID-19 and future roadblocks. IQVIA encourages sponsors to see the pandemic response not as a single event, but as an ongoing, evolving process that must be measured and routinely updated to meet patient needs.

The pace alone to keep up with shifting numbers of sites and patients available on a regional basis affects adaption strategies. An example of varying figures is site closure rates, which may differ per regions and countries. In some areas, access to sites may be a possibility on a limited basis, and in others, site visits are not an option to patients or staff. The majority of sites in all major regions, including the U.S., Europe, Asia, and Latin America, were either closed or under severe restrictions, causing adjustments to virtual approaches to evolve quickly (Figure 1). To meet the changing needs in each country and region, sponsors will require a well-prepared partner with the global and local expertise and tools in place, as well as the operational bandwidth and agility, to implement new processes.

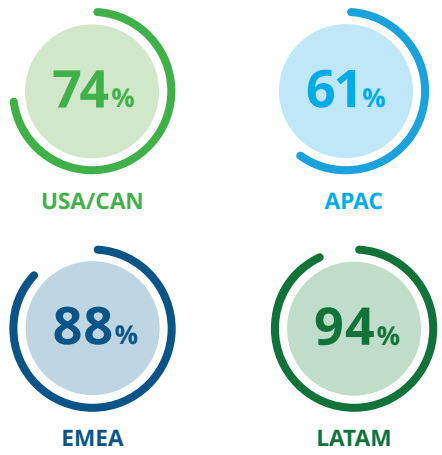
Additionally, despite overarching regulatory support, guidance and regulations still differ per countries and regions, making a tailored approach that quickly and effectively evaluates risk and needs at the individual study level vital to keeping trials moving forward. Identifying risks and developing mitigation strategies for each stage of the project lifecycle have to be considered before making adjustments to any trial model.

At IQVIA, we established a COVID-19 risk assessment workflow, powered by dedicated teams whose sole

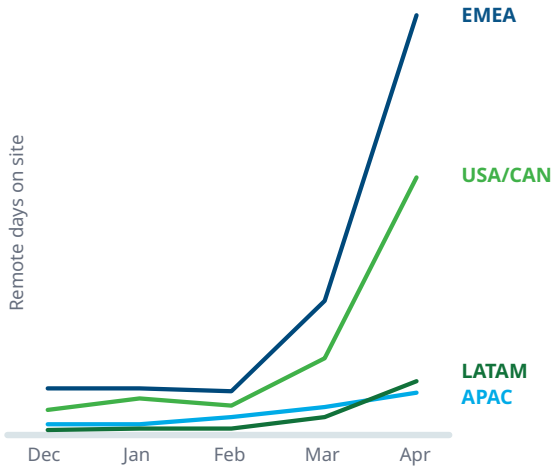
focus is to monitor COVID-19 regulations to interpret their potential impact to current and future studies, and advise sponsors and study and site teams on how to adapt. These workflows use decision trees, templates, and instructions to help sponsors conduct initial risk assessments, including gauging appropriateness of remote visits and monitoring, shipping investigational product, and more.

The study teams, in conjunction with subject matter experts, assist in the deployment and assessment of these mitigation strategies, and continually monitor newly issued regulatory guidance to update these tools.

Figure 1:Early % of sites with no CRA visits permitted



Virtual days on site



Source: IQVIA Internal Trial Analysis. Data as of April 14th, 2020

Switching models: Key components

Viewed as an opportunity to innovate and drive new thinking in trial execution, a holistic approach is being used by partners to help sponsors maintain trial continuity so sponsors can:

- Stay focused on continued clinical development
- Lower the burden of trial participation for patients and site teams
- Open the doors for more diverse patient population participation
- Enhance patient engagement

These new approaches include critical elements such as data-driven processes, advanced analytics and technology-enabled solutions leveraging artificial intelligence and machine learning to enhance deep domain expertise, virtual or decentralized trials, telehealth, and direct-to-patient recruitment.

REMOTE MONITORING

Patient safety is always the top priority for sponsors and research teams, and COVID-19 has heightened this concern even further. By adopting remote monitoring processes with a risk-based monitoring model, along with innovative technologies and advanced analytics to maintain data oversight, sponsors can address the challenges of reduced site staff and inability of CRAs who physically visit sites to monitor trial activity and data.

Remote monitoring solutions can offer a central repository for data and automated workflows that allow Clinical Leads and CRAs to identify signals and monitor safety trends across sites, regions, and participants within a fully traceable environment without stepping into a trial site. Early detection of signals enables faster resolution of issues, and predictive analytics can identify where problems are likely to occur, presenting ways to preempt potential issue occurrence.

With the current situation, today's analytics tools enable study teams to combine current insights with the impact of the pandemic on individual sites and help develop a comprehensive response strategy, including risk assessment. This assessment aims to evaluate and determine risks from the site, patient and overall trial perspective. Being able to continually monitor and identify signals and trends, including risks, early on can help maintain patient safety and data integrity.

Traditionally, key risk indicators or KRIs such as adverse event rates, protocol deviations, overdue action items and more are the base for monitoring and related operational planning and adjustments. Currently, the pandemic adds several layers of risks to consider when examining analytics metrics such as levels of site access and patient participation and changing COVID-19 information per geographies.

Figure 2: Site risk analytics

SDV backlog

COVID-19 information

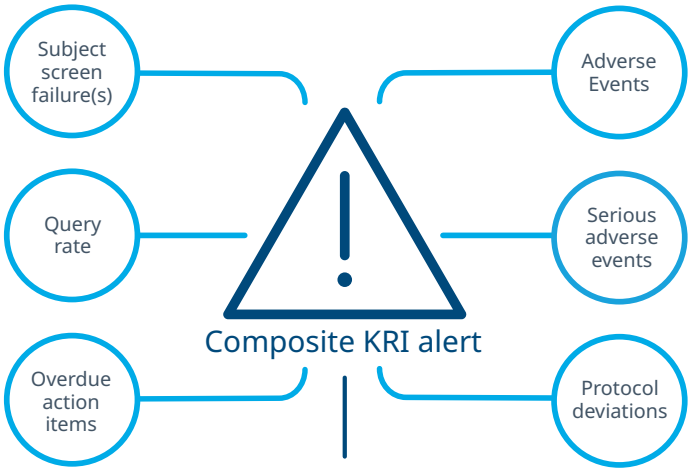
Site access and

Patient participation

Composite KRI:

- Adverse event rate
- Serious adverse event rate
- Protocol deviation rate
- Overdue action items
- Query rate
- Screen failure rate

A group of selected metrics, along with the ability to use concepts of "data recency" (the algorithm looks at last three months of data instead of project-to-date metrics) and "weightage" to help in identifying specific risks to address



Monitoring Key Risk Indicators (KRIs)
With adequate support from remote monitoring, KRIs can be monitored by one or more monitors based on operational planning

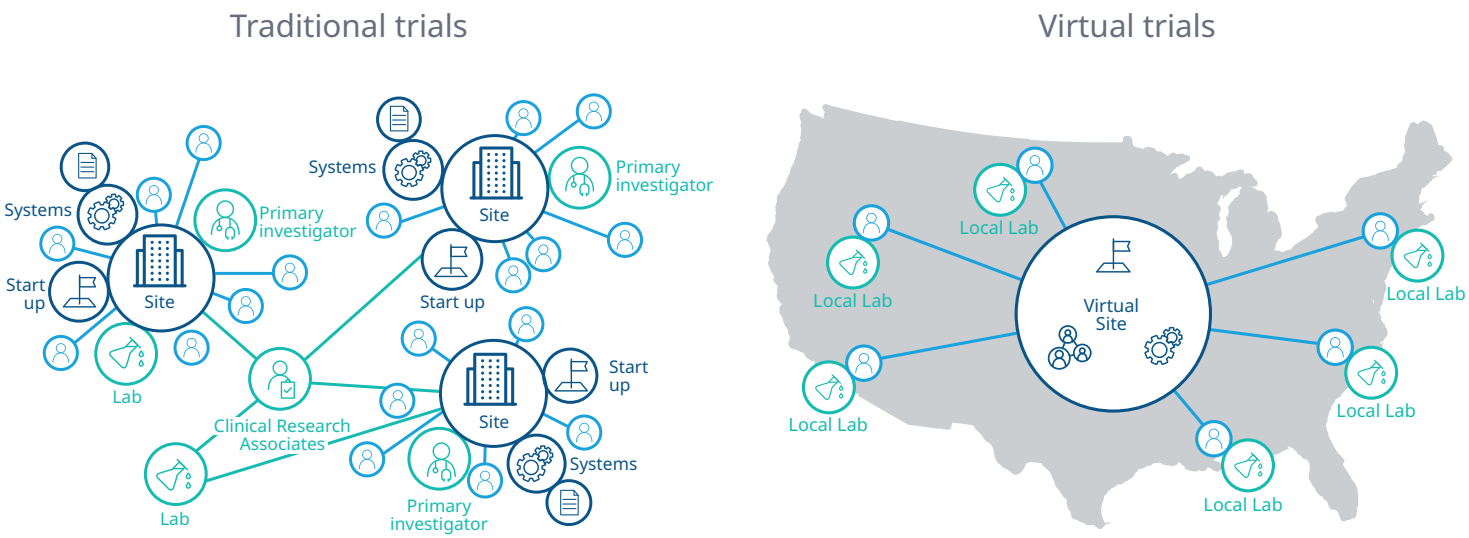
When adopting a detailed remote monitoring approach, sponsors must keep in mind that their approach is compliant with data privacy regulations in the countries where their trials are operating. Additionally, they will need to work in support for the increase in data sharing and storage at each site.

VIRTUAL TRIALS

Patients today are far more savvy and engaged in their healthcare than in the past, and sponsors are valuing stronger partnership with patients than ever before. When experiencing obstacles like a global pandemic, it is even easier to recognize the importance of keeping patients engaged, educated, and in the loop throughout the trial and afterwards, especially as site access is limited or unavailable. Reducing their burden is critical to maintaining trial continuity during COVID-19 and post-pandemic.

For years, there has been a focused effort on developing, refining and delivering decentralized patient-centric trial design. In combination with remote monitoring capabilities, virtual trials provide flexibility that is urgently needed during times like these to essentially bring trials to patients in the comfort of their homes. When building a trial protocol around patients, sponsors are able to more strategically rethink how they will engage with patients to improve recruitment and retention.

Figure 3



A new Study Hub technology platform underpins virtual trials solutions by offering the patient support and visibility throughout their trial experience under one comprehensive and highly secure resource. Study Hub is the center of a patient's trial experience, and it supports primary investigators or PIs and site staff by serving as a one-stop for data is capture and ongoing communication between patient and site teams.

Televisits

Compliant with local patient privacy regulations, patients are participating in trials via televisits with virtual study teams and PIs. Study teams are keeping patient assessments on track to prevent the loss of vital data when facing challenges such as the pandemic.

In support of these visits, study teams can determine what peripheral tools are necessary such as electronic diaries and questionnaires to collect patient reported outcomes. 24/7 online chat options and follow-up visits are available to patients to ensure their questions, concerns, and trial needs are met. Additionally, connected devices including wearables that help monitor patient progress can be incorporated to capture data remotely.

As continuous data is collected and stored from various tools in place per trial, remote monitoring with advanced analytics can help detect early signals of risk. If there are protocol amendments during the study, patients can complete updated consent documents electronically to ensure progress is not stalled.

Staff training

As more virtual elements are integrated into trials, it is vital for sponsors to assess their trial sites' capacity to support the increase in data sharing and storage and evaluating internet speeds to ensure they can support a telemedicine platform.

On the same note, staff must be trained to use the new technology and data platforms. In a virtual setting, staff will also adapt their patient engagement strategies to looks for cues and signs of additional support the patient may need based on observing the patient in their own home and more.

Home visits and direct-to-patient services

At times when it is not safe for patients, especially high-risk populations, to visit sites or labs, reevaluating trial protocol needs is key to assessing how to shift to a virtual model specifically. Sponsors can work to identify and potentially eliminate lab testing and other evaluations that are not critical to meeting endpoints. Once that step is in place, pinpointing what logistical gaps need to be filled to meet trial objectives will help determine what virtual elements are set in place.

To ensure patients can limit activities outside of their homes, trained healthcare professionals, including nurses and phlebotomists, can conduct home health visits to perform lab work, infusions, or other home care needs.

For example, to help ensure study continuity of a highly complex and challenging phase 2b study where many assessments needed to be conducted at a physical site, elements of virtual trials were introduced. A thoughtful and quick response plan resulted in the removal of two office-based patient assessments that were not critical and the completion of 47 home health visits for drug delivery and lab testing.

It shows that though some studies will require face-to-face contact, but we can eliminate the need of visiting a trial site. In cases where a patient must go to a lab or hospital, sponsors can coordinate with concierge services that specialize in safely transporting vulnerable patients. Additionally, as needed, supplies, medications, and other needs can be directly shipping to patients to avoid leaving the home.

Figure 4: Scalable, adaptable virtual models

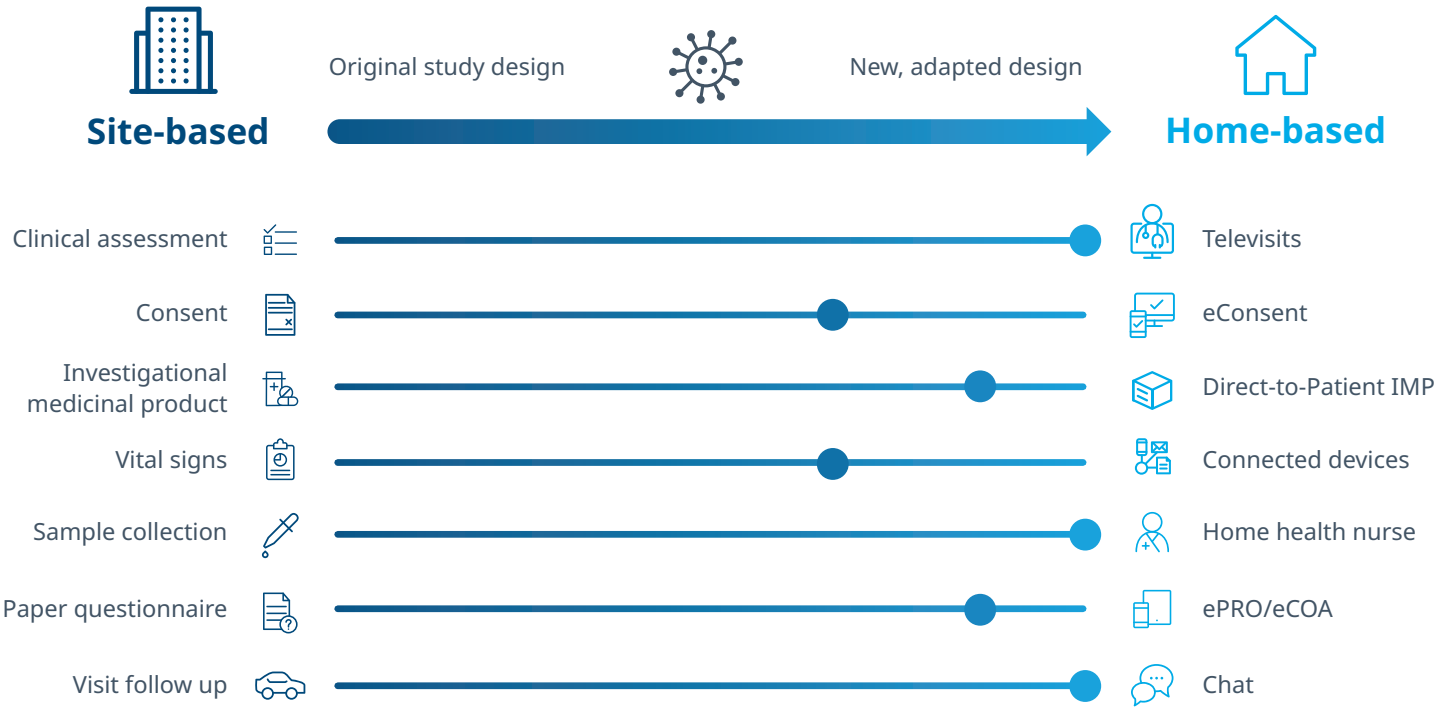


Figure 5: Rapid response

Challenge

- Highly complex and challenging study with many assessments that needed to be conducted at a physical site
- Due to COVID-19, patients cannot travel to sites and sites cannot perform all assessments

2
office-based patient assessments removed

Response

- Protocol simplification – Reassessed the protocol and removed study activities that were not critical
- Patient diaries – Moved to electronic patient reported outcomes (eCOA) for electronic diary entries
- Drug delivery and lab assessments – Implemented drug delivery and home-health services for at-home administration and lab draws
- Remote visits – Pushed to telehealth visits to ensure continuity of contact between site and patient

1
week to convert to electronic diaries

Results

Rapid response ensured study continuity

47
home visits completed

Source: IQVIA COVID-19 Executive Briefing

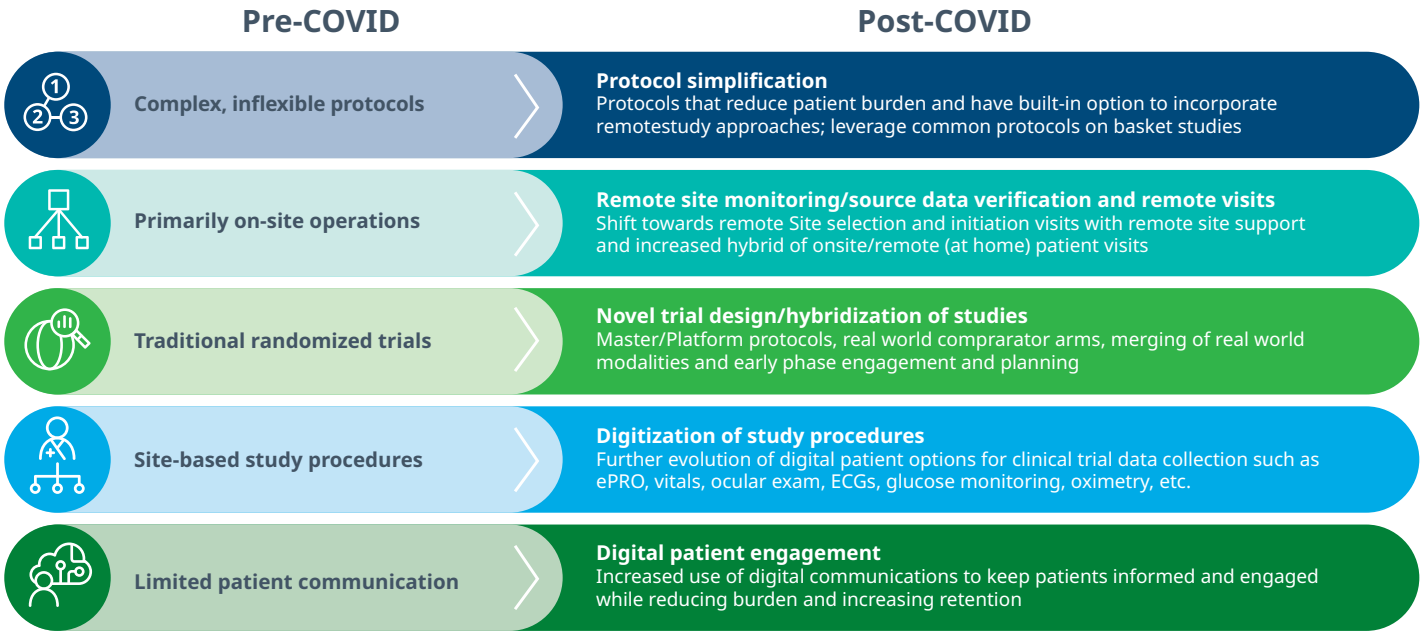
Conclusion: shaping the future of research

COVID-19 is not the first pandemic we have faced, and it will not be the last. Time will tell exactly in what directions it will push clinical development, but it has shown the industry that accessible and adaptable clinical trial models are necessary, and the broader use of remote clinical trials technologies and approaches, underscores their value in patient engagement and retention while maintaining patient safety and data quality.

Innovation is accelerating and paving the way for a new normal, including patient-centric design and enhanced technological infrastructure. In a recent survey[1] of clinical sites throughout the U.S. and Canada, sites identified Remote Access Technology, including eSource, eReg, eMR and Telemedicine as having the highest major impact on what would help during these situations.

Technology is impacting nearly every aspect of clinical trials, from simplifying protocols, improving site selection and remote monitoring, to digitizing procedures and enhancing patient communication.

Figure 6: Accelerated innovation is paving the way for a new normal



Trial models can now better account for anticipating roadblocks and making real-time adjustments quickly, so, research around needed therapies are not at a standstill. As long as reviews and considerations are made at individual trial levels, incorporating remote monitoring capabilities and scalable virtual trial elements can help maintain trial continuity and reduce patient and site team burden now during a global pandemic and into the future, as clinical development continues to transform and adopt digital solutions.

[1]Source: IQVIA U.S. and Canada Site Survey 2020 (n=138)

About the authors

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Rajneesh Patil is Vice President, and Head of Process Design, Technology & Advanced Analytics for Risk Based Monitoring, leading a team to provide an industry-leading, technology driven RBM solution for over 10 years.

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