PCM TRIALS
QUALITY MOBILE RESEARCH

How Sponsors and CROs can Fully Benefit from the Permanent Shift to Decentralized Clinical Trials Brought About by the COVID-19 Pandemic

EXECUTIVE SUMMARY

Evidence is mounting that hybrid and decentralized clinical trials are here to stay. What was once a nice-to-have is quickly transforming into a must-have. As reported in *Clinical Trials Arena*[1], roughly 1,300 clinical trials with a virtual and/or decentralized component will begin in 2022, representing a 93% increase over 2020. And in a recent Industry Standard Research (ISR) survey[2] of clinical trial sponsors and CROs, more than 80% of respondents said they expect the hybrid model to be used more often than the traditional trial model within the next three years. The catalyst for this dramatic shift was the COVID-19 pandemic when, to avoid over-burdening hospitals and healthcare facilities, many non-essential clinical trials were deferred.[3]

The new normal for clinical trials will demonstrate a shift in design and protocols to embrace redundant pathways, including the home-care model that survived the test of COVID-19.

To aid sponsors and CROs in fully realizing the benefits of decentralized clinical trial methods moving forward, this whitepaper extracts the lessons learned from the pandemic and their implications for clinical trials now and in the future.

During the early months of the pandemic, clinical trials that relied heavily on participant visits to investigator sites were most at risk as non-essential travel was discouraged and citizens were instructed to remain at home—especially immunocompromised people. During this period, the Clinical Trials Transformation Initiative (CTTI), a public-private partnership to improve

the quality and efficiency of clinical trials, recommended that trials "pivot" to remote protocols, including the use of virtual and home health services.[4]

Based on lessons from the pandemic, it is clear that clinical trial designs and protocols should utilize redundant pathways that include a significant home-visit component that can be scaled on relatively short notice. These findings signal the emergence of a new normal for clinical trials—an acceleration of the shift away from site activity to home-based services wherever possible.

PRE-COVID-19 CLINICAL TRIAL STANDARD OPERATING PROCEDURES

Clinical trial sponsors and contract research organizations (CROs) face significant challenges when it comes to maintaining participation over the course of a lengthy trial. Even in the pre-COVID-19 "old normal," dropout rates averaged around 30%[5] —often because participants found their periodic site visits to hospitals and health centers to be stressful experiences.[6]

Of course, participant site visits are necessary when clinical trial protocols require physician services and access to non-mobile equipment. Additionally, in most cases, initial diagnoses, enrollment, screening and assessments are done at the site.

However, for many activities related to clinical trials, interacting with participants away from the clinic is appropriate and even advantageous from a participant's perspective. Many trials design their protocols with that in mind, utilizing specially trained Registered Nurses (RNs) who routinely visit participants' homes to manage a wide variety of services critical to the trial.

It is important to understand the range of clinical trial services these RNs can and cannot offer in a home visit. In some cases, the limits are a function of the home setting itself and the equipment required. In other cases, there are certain services RNs are simply not licensed to perform, whether in or outside the healthcare facility.

Those limitations are relatively few, though. In the course of home visits, RNs routinely collect lab samples, administer the investigational medicinal product (IMP), perform drug accountability, interview participants and collect vital signs data. They offer the added value of being the eyes and ears of the clinical trial team, noting developments or unusual symptoms.

The Certified Mobile Research Nurses (CMRNs) at PCM TRIALS can perform most in-scope clinical activities as long as they can utilize portable equipment and maintain

an acceptable level of risk for the participant and themselves. Here is a broad outline of the types of activities a CMRN can perform in a home environment:

- Assess the subject (e.g. adverse events and concomitant medications)
- Administer the IMP (oral, infused, injected, inhaled and topical)
- Draw specimens (blood, urine and saliva)
- Conduct lab tests using point-of-care tests or processing samples and shipping them to a laboratory
- Use equipment such as centrifuges, infusion pumps and ECGs
- Complete source documents
- Conduct surveys or questionnaires
- Educate participants
- Address other approved "outside the norm" requirements

In spite of this, too many sponsors and CROs only utilize the home-based option sporadically—historically for rare or orphan disease studies and cases where travel distances to investigator sites or poor health limit a participant's willingness or ability to travel.

HOW DID COVID-19 IMPACT CLINICAL STUDIES?

COVID-19 changed many aspects of healthcare: how best to protect caregivers, the need to stockpile critical supplies and, yes, the optimal management of clinical trials.

Clinical trial home visits previously had been viewed in many cases as "nice to have." Seemingly overnight, though, home-visit services became "need to have" elements of clinical trials. They could potentially serve as vital extensions of site-based activity as more and more studies were at risk due to two factors that, in hindsight, always should have been seen as concerns.

Limited access to hospital sites. As the scope of the COVID-19 threat became more apparent, many of the hospitals that served as clinical trial research sites were closed to all but essential COVID-19-related services.[7] Due to increased risks to study participants and the limited availability of clinical staff at the sites, clinical trial participant screening, enrollment and monitoring activities in those locations came to a halt for many studies.[8]

Participant quarantines. Within weeks of the COVID-19 outbreak in the United States, most people, including clinical trial participants, were staying at home as instructed by public health officials and government authorities. Thus, even if a specific study referral center remained open for clinical trial activity, participants were often not willing to travel—especially to any location related to healthcare.

THE U.S. FOOD & DRUG ADMINISTRATION (FDA) RESPONSE

In a Guidance document issued early in the pandemic, the FDA acknowledged that the COVID-19 pandemic could negatively impact clinical trials, not only for the reasons cited above, but also due to interruptions in the supply chain and COVID-19 infections among site personnel and participants.

The agency gave sponsors the latitude to work closely with their Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) to amend their study protocols in ways that would protect the safety of participants. In the Guidance, the FDA recommended that administrators consult with "...FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel).[9]

HOW DID CLINICAL TRIAL SPONSORS RESPOND?

In the case of trials whose protocols were centered around investigator sites, sponsors faced a dilemma. As noted above, many non-essential studies that were in their early stages were cancelled or postponed. Other sponsors, especially those with trials that were near completion, attempted to engage home-visit clinical testing service providers. These providers, including PCM TRIALS, accommodated sponsors and CROs as best they could, but these companies faced two major hurdles related to onboarding clinical studies mid-trial at that point in time:

First, there are significant Good Clinical Practice-specific "bridge-building" steps for establishing home-visit clinical trials. On-boarding a study, whether new or in progress, typically requires weeks, not days. Nurses must be trained for novel situations so they can accurately and compliantly carry out their work with the necessary equipment on hand. The training programs themselves must be approved by the sponsor. Thus, home-visit clinical trials are not "last minute bolted on" solutions. Corners cannot be cut.

The fate of clinical trials during COVID-19 largely depended on the extent the sponsors had relied on site-based vs. home-visit participant follow up.

Second, home-based clinical trial service providers were already working at or near capacity, serving their clients who had built this dual pathway into their trial designs. This work, incidentally, proceeded essentially uninterrupted throughout the pandemic. Thus, the fate of clinical trials during COVID-19 largely depended on the extent to which sponsors had relied on site-based versus home-visit participant follow up. The findings are summarized in the table below.

The Fate of COVID-19 Era Clinical Trials as a Function of their Reliance on Site vs. Home Visits

Trial Type	Description	Impact on Clinical Trial
No Home Visits	Clinical trials have no home visit or alternate pathway around site-level execution.	***High impact on trial.*** Sites are shut down or patients stay at home. Alternative resources are sought to rescue, but difficult due to lack of infrastructure and experience with home visits.
Minimal Actual Home Visits	Clinical trials that have minimal home visit component, or home visits available but not broadly leveraged, e.g. low utilization.	***Medium impact on trial.*** Sponsors/CROs offer some home visit options, but they were often bolted onto the protocol afterwards, and the adoption was not broad based. Steep learning curve by everyone that can at times feel like a rescue.
Regular Home Visits	Clinical trials operating with home visits.	***Lower impact on trial.*** Sites are already familiar with home visits, which were built into protocols, processes, documentations, and logistics. Ability to scale is high.

CLINICAL TRIAL LESSONS LEARNED FROM THE COVID-19 EXPERIENCE

The phrase "new normal" is being used, and possibly over-used, in many contexts these days as the number of COVID-19 cases has declined and social distancing directives have been relaxed.

But for the clinical trial industry, there certainly should be a permanent shift in how home-based service is incorporated into clinical trial protocols. Before COVID-19, immunocompromised and fragile patients were expected to travel to potentially risky study sites for routine activity, such as blood draws or rudimentary dosing.

The new normal for clinical trials should be informed by the following lessons learned during the COVID-19 pandemic:

1. ***Clinical trials without a home-visit pathway were unable to simply add on a home visit alternative solution at the last minute.*** As noted above, whether at its start or in mid-trial, the use of home visits comes with a steep learning curve for both the sponsor and the home-visit service provider since each trial is different and must be precisely planned and managed.
2. ***Clinical trial studies that included home-visit protocols from the beginning fared well.*** Scaling up home visits was far easier when the protocols included a significant level of home-based

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service from the start. Clinical trials that ignored the home-visit option, or considered it a low priority, were the most vulnerable since it is not easy to scale from zero or near-zero in the midst of a global pandemic.

3. ***Human beings are increasingly in tune with self-preservation.*** The general population was transfixed by images of overcrowded COVID-19 patient facilities and healthcare professionals working tirelessly in full Personal Protection Equipment. While the situation has become less dire, the emergence of new variants has led many people to continue to avoid places that expose them to the risk of infection. Imagine, then, the new outlook of clinical trial participants who may be immunosuppressed and fall into the now familiar category of people with "underlying health conditions." Increasingly, the clinical trial industry will need to consider shifting toward protocols that involve home-based interaction.

THE NEW NORMAL IS A SHIFT

Home-visit clinical trials are not new. To obtain the data they need, forward-thinking sponsors and CROs have been meeting their patients more than halfway—not just in their homes, but even in their workplaces and travel destinations.

The COVID-19 experience simply reinforces the fact that clinical trial models that interface with participants where they live not only offer access to a more diverse population, but the studies are somewhat insulated from healthcare crises that can preoccupy an on-site trial center and the supporting healthcare team.

Thus, the new normal for clinical trials is not a sea change. Rather, the new approach will be a conscious shift in clinical trial design and protocols. Where possible, clinical trials will incorporate the home visit model that survived the test of COVID-19.

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[2] ISR Reports (2021, July). Clinical Researcher: Preparing for the Future: Data Collection and Technology Deployment in Decentralized Clinical Trials. Retrieved from https://acrpnet.org/2022/02/15/preparing-for-the-future-data-collection-and-technology-deployment-in-decentralized-clinical-trials/.

[3] Weintraub K. (2020, March 31). COVID-19 Slows Drug Studies, Curbs Clinical Trials. WebMD Health News. Retrieved from https://www.webmd.com/lung/news/20200331/covid-19-slows-drug-studies-curbs-clinical-trials.

[4] The Clinical Trials Transformation Initiative. (undated). Best Practices for Conducting Trials During the COVID-19 Pandemic. Retrieved from https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/best_practices_for_conducting_trials_during_covid_041320.pdf.

[5] Retention on Clinical Trials – Keeping Patients on Protocol [Infographic]

[6] 2013 Perceptions & Insights Study – Ineligible Participants and Those Who Drop Out

[7] Kaplan GA, Weaver R, Cloud B. (2020 April 21). Supporting Clinical Trial Sites During the COVID-19 Pandemic. *Applied Clinical Trials*. Retrieved from http://www.appliedclinicaltrialsonline.com/supporting-clinical-trial-sites-during-covid-19-pandemic.

[8] Lupkin S. (2020, April 11). Coronavirus Pandemic Brings Hundreds Of U.S. Clinical Trials To A Halt. *Shots: Health News from NPR*. Retrieved from https://www.npr.org/sections/health-shots/2020/04/11/832210606/coronovirus-pandemic-brings-hundreds-of-u-s-clinical-trials-to-a-halt.

[9] U.S. Food and Drug Administration. (2020). *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*. March 2020, updated 14 May 2020. p.7. Retrieved from https://www.fda.gov/media/136238/download.

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