Navigating Evolving Trends in Clinical Research

QUADRIGA PARTNERS

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Preface

The gross disparity between human capital supply and demand in the wake of the pandemic has crippled current operational capacity and future growth of businesses across all sectors of the economy. Although the impacts have been felt at all levels of workers, from the C-suite down to entry level positions, the shortages are perhaps most acute at the middle management level. There are many factors which have been put forth as the root causes, from burn-out to increased mobility in the WFH / hybrid model adopted by some sectors to the overall intensity of economic activity in a growth environment, which all create labor market tightness. Higher than comfortable levels of inflation add a new wrinkle to the equation; with declining margins employers have less excess free cash flow to dedicate to proving economic incentives for recruitment and retention.

Within pharma services, labor shortage is by far the number one issue faced by business owners. Demand from pharma is unrelenting, however, growth is constrained by the inability to recruit additional coordinators, managers, and other key administrative staff personnel. There is a pervasive sense of dread surrounding what might happen should a key employee depart. We have heard anecdotes about certain smaller pharma service businesses needing to close operations, sadly, because of these shortages. Businesses which continually invest in technological enablement processes will outperform competitors in both the recruitment and retainment of mid-level high performers.

About Quadriga Partners

Quadriga Partners is a premier healthcare investment bank, providing merger and acquisition advisory and growth and debt capital raising services exclusively for healthcare companies. Quadriga has a particular emphasis on several key sectors, including outsourced pharmaceutical services, and is among the most active advisors for clinical research focused transactions. Quadriga begins by obtaining an intimate understanding of their client's short and long-term objectives.

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30% of employees who left the workforce in 2021 cited “unsustainable work performance expectations” as a top reason for leaving

While market pressures tend to naturally drive in the direction which lead to the amelioration of labor shortages, the market response is often extraordinarily prolonged. Businesses who merely ride the rising tides will lose talent to organizations who are proactive in finding the right steps to improve employee retention and recruitment rates. Although causes for labor shortages are complex and multivariate, solutions to remedy the prevailing effects can be bifurcated into (i) increasing retention and (ii) decreasing the number of workers needed per unit of production.

Although an acceptable level of turnover is not straightforward, as some turnover linked to low-performing employees can be healthy for an organization, clinical research sites typically rely on a small number of employees who are responsible for a wide variety of tasks, making each employee tremendously valuable. The negative effects of turnover can subsequently spill over into the retention of subjects in clinical trials, as trial subjects who have developed a relationship with site staff may lose motivation to continue once that personal connection is absent. In addition, high turnover rates lead to less experienced employees staffed on important clinical research trials. Although errors in clinical research can happen at any level, it’s important to note that meaningful errors that contribute to trial failures, such as participant qualifications and protocol deviations, all happen at the site level.

Alarmingly, there has been a limited amount of research conducted surrounding the methods or tools used to measure workload in the clinical trial setting. Historically, research managers of clinical trials have relied primarily on intuition and experience for estimating staff capacity for allocation of work assignments. Ultimately, when aspects of workload are not measured, finding equilibrium in workflow for CRAs can be near impossible; while CRAs oscillate on the workload pendulum, the integrity of the clinical trial is at stake.

Early studies on the topic of workload reveal the sub-optimal effects of workload that is either too high or too low. Humans faced with overbearing workloads are more prone to rushing through tasks, committing more errors, and becoming frustrated and fatigued. Interestingly, humans who are underworked can exhibit many of the same symptoms. Coincidentally, over 30% of employees who left the workforce in 2021 cited “unsustainable work performance expectations” as a top reason for leaving.

Figure 1

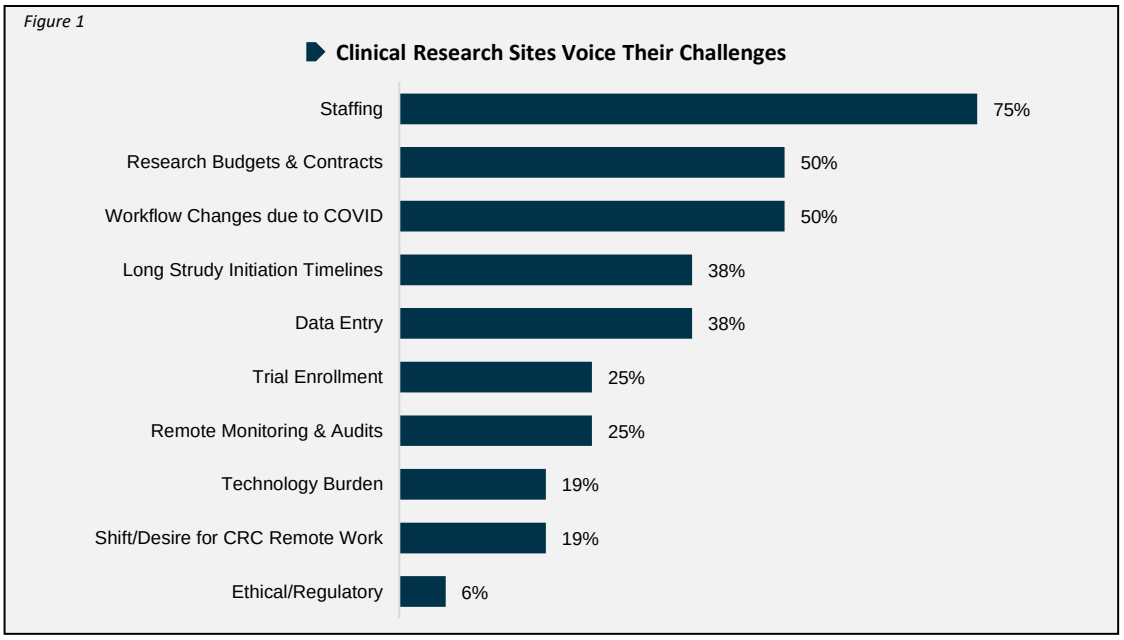
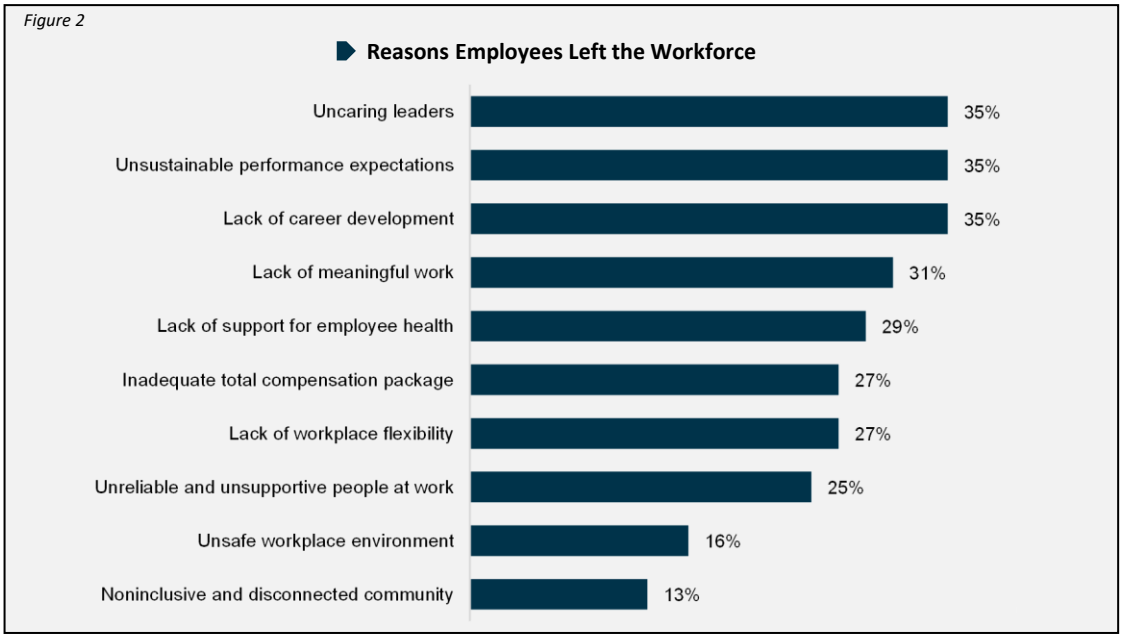


Figure 2

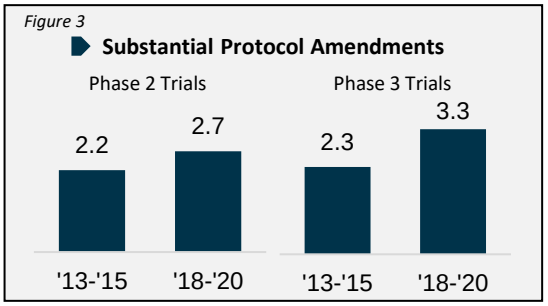


Tailwinds from drug development post-COVID has led to record demand for trial starts while headwinds from the great attrition paired with increased trial complexity limit site capacity and prolong trial duration

Clinical research sites are innately complex institutions. Investigators are tasked with navigating constantly changing regulatory requirements and inclusion criteria, managing large amounts of data from various sources, and consistently monitoring and examining patients – which is entirely dependent on successfully recruiting patients in the first place. Recent trends are showing an even greater amount of trial complexity coupled with record overall demand. An analysis that was based on 9,737 clinical trial protocols approved between 2001 and 2015 showed a significant increase in the number of distinct procedures and total procedures performed for each patient in different phases of a trial. More recently, the mean number of deviations and substantial amendments per trial has increased across all trial phases. The implication of additional amendments is longer trial lengths and greater costs; the CSDD estimates that just one phase 3 protocol amendment costs $535,000 in direct unbudgeted costs and an additional three months of unplanned implementation time.

Investigators have been caught driving through the perfect storm. Tailwinds from drug development post-COVID has led to record demand for trial starts while headwinds from the great attrition paired with increased trial complexity limit site capacity and prolong trial duration. Research shows that a main driver for employees leaving the workforce is being overworked. As trial volume, length, and complexity increase, CRAs are tasked with heavier workloads and trial participants are expected to endure longer and more involved trial periods. The list of competing priorities and challenges for principal investigators is long-winded; ultimately, investigators who continually evolve and create unique strategies to retain employees and trial participants will attract to most attention from sponsors, CROs, and investors.

Figure 3



Tech Enablement Driving Efficiency at the Operations Level

Rapid Adoption of eConsent – From its inception in the 1960s up until present day, the process of written consent has undergone extraordinarily little change. Once viewed as a novel functionality, recent changes in the industry landscape have increased the need for eConsent as a standard for clinical trials. The COVID-19 pandemic was a major catalyst in the adaptation of eConsent. At the end of 2020, 47% of research sites were utilizing eConsent applications. As of July 2021, 57% of research sites used eConsent applications. Of the remaining sites who have not adopted eConsent, 18% plan to integrate some form of remote consent in the future. As research centers closed, teams working on in-progress studies needed a method to re-consent participants due to protocol amendments, objections to adoption were overcome by necessity.

The pandemic may have been the straw that broke the camel's back in terms of forced adoption, however, various other parts of the transition away from written consent were already underway. The most identified business drivers for implementing eConsent were patient comprehension, efficiencies through digitation, and patient retention. As the paradigm shift continues from small molecule to large molecule therapeutics, clinical trials are forced to target significantly smaller, more complex patient populations, making recruitment and retention more costly.

One of the most common issues patients cite for dropping out of trial studies is feeling unclear about their role in a study

As the scope narrows for qualified trial participants, the stakes rise for the retainment of recruited patients, which on average face a dropout rate of 30%. It's estimated that sponsors lose $600,000 to as much as $8 million for every day a clinical trial is delayed. With costs being so high, there are massive gains to be made by improving the rate of recruitment and retention.

Increasing Valid Consent – One of the most common issues patients cite for dropping out of trial studies is feeling unclear about their role in a study. It's important for participants of clinical trials to fully comprehend the risks and benefits of a clinical trial before deciding whether they wish to consent to it. For the vast majority of the population, the clinical trial landscape is foreign territory. Traditionally, written consent forms lack readability and simplicity which can further patient confusion. Digital versions of informed consent can communicate clinical trial information in easy-to-understand formats by including features such as videos, interactive images, and audio recordings.

Figure 4

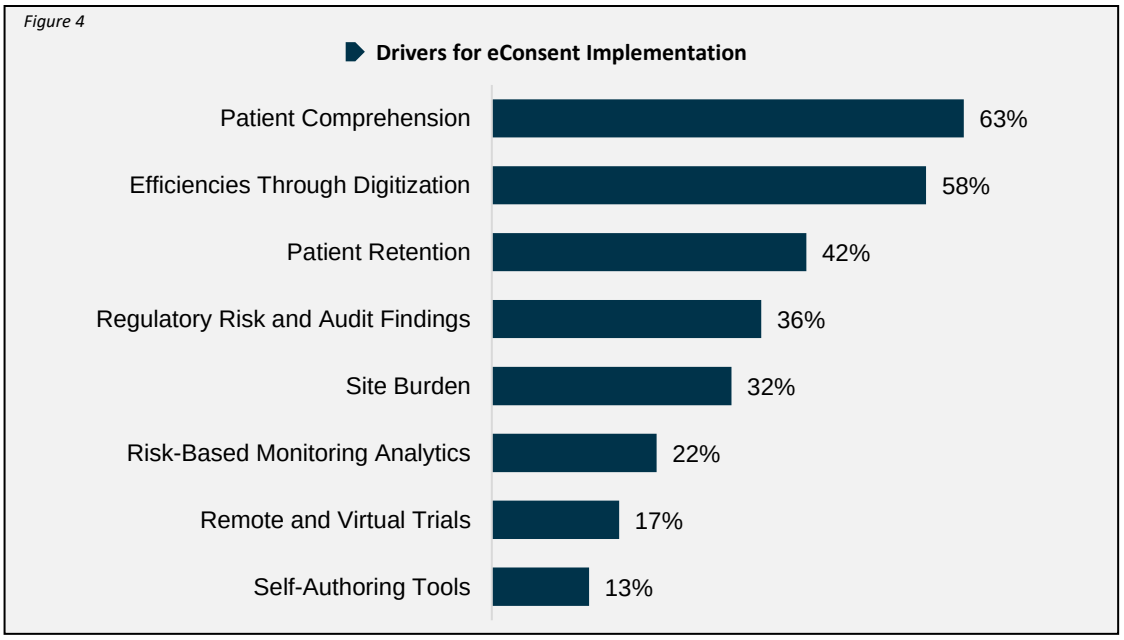
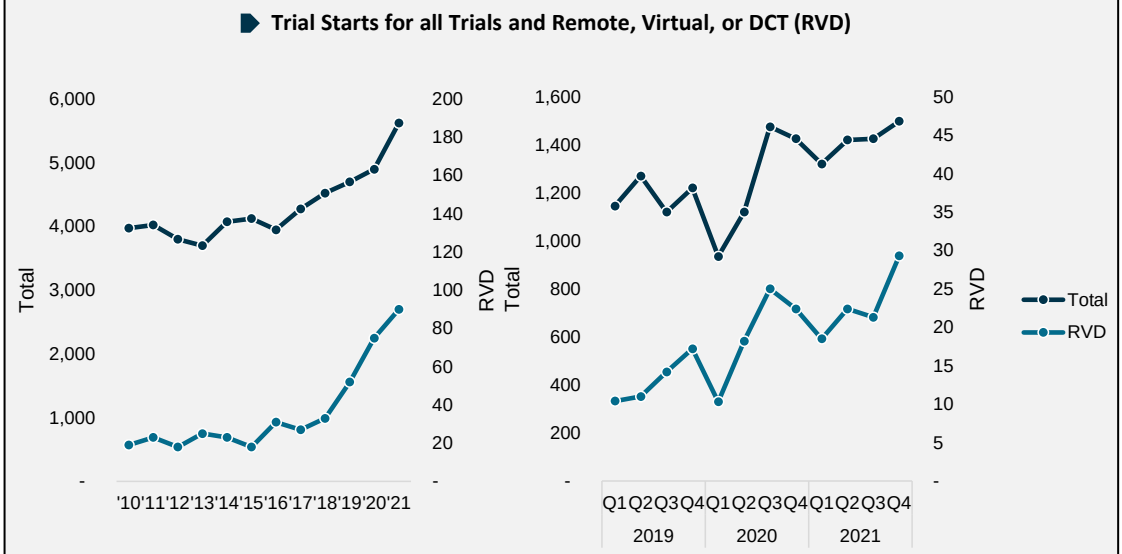


Figure 5



Uses of EDC – Sponsors need to know where sites and participants are in the enrollment process to identify delays and potential risks. With automated data reporting built in to some eConsent programs, sponsors have the ability to run automated edit checks on the completeness of ICFs and trigger alert messages in the case of eConsent errors. Unfortunately, sites can mistakenly move along in the trial process without getting a valid ICF first, resulting in the data being invalidated and ultimately rendered useless. Invalidity is compounded by transcription errors from written ICFs, which can be automatically updated into the EDC system from electronic alternatives.

Adoption Rise and Challenges in Decentralized Trials

As the ecosystem for drug development continues to evolve and clinical trial sites continue to recover from the impact of COVID, an increasing number of decentralized elements beyond eConsent have been introduced into trials.

Clinical trial sponsors were already using many of the components of DCTs before the onset of the pandemic, without becoming fully decentralized. The use of remote, virtual, or decentralized elements has accelerated in the past three years, with early 2020 seeing a very sharp increase in decentralized methods that mirrored a sharp increase in total trial activity. Although the 2021-2022 growth curve for decentralized methods attenuated slightly, the last quarter of 2021 showed the highest quarterly utilization yet, suggesting a continuing industry wide adoption moving forward.

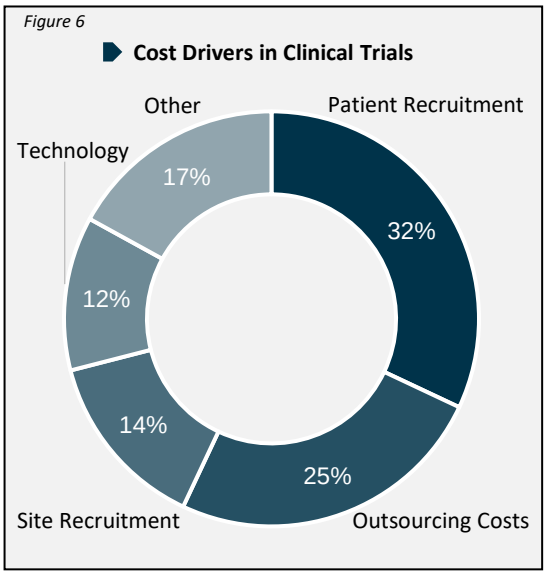
86% of all trials do not meet certain enrollment timelines and 30% of phase 3 trials fail due to enrollment challenges

Traditional clinical trials often centralize operations at specialized centers far from where most patients live. In the U.S., the median unidirectional distance traveled to a clinical trial site is more than 25 miles, representing a total travel distance of over 50 miles to a clinical trial investigator site. In a global survey of over 1,600 patients, 42% cited “travel inconvenience” as the main reason for declining trial participation, surpassing “drug side effects” by 12%. One of the greatest benefits of decentralization is the improved logistics in conducting clinical trials. As clinical trials become more complex in response to drug development innovations, a greater need for larger, more diverse pools of study participants surfaces. A patient may be ineligible to participate due to their medical history or a mismatch in the stage of their disease compared to the trial protocol. These challenges can compound to create delays to the extent that 86% of all trials do not meet certain enrollment timelines and 30% of phase 3 trials fail due

to enrollment challenges. The convenience of remote and virtual data collection harnesses the potential to improve patient recruitment, retention, and engagement.

Virtually connecting an industry with deep roots in centralization doesn't come without challenges. Although tools such as electronic consent, telehealthcare, remote patient monitoring, and electronic clinical-outcome assessments (eCOAs) allow investigators to maintain links to trial participants without in-person visits, sponsors and site investigators must choose which decentralization tools are appropriate for their unique study. The diverse set of options available allow for a broad spectrum of decentralized and hybrid clinical-trial designs. In the near term, sponsors, investigators, and research service providers expect fully virtual trials to remain limited to a narrow set of use cases.

Figure 6



Juxtaposed with DCTs, centralized studies can be comparatively straightforward to manage for investigators. Drug distribution and management becomes entirely more complex when drugs must be shipped to multiple coordinating sites and potentially directly to patient homes. For trial drugs to be shipped to patient homes appropriately, there must be assurance of drug stability and suitable temperature-controlled storage facilities, methods to prevent unauthorized access and tampering, proper dosing documentation to record dosing, and communication between the storage system and the drug source to provide timely refills and prevent study interruptions.

Navigating the complexities of drug shipping and management introduces potentially greater risks to both subjects and the integrity of the trial.

Additionally, remote based clinical trials may not be appropriate for all types of clinical research, namely translational and dose-finding studies which require frequent interventions such as dose modifications and serial tissue biopsies. Traditional trial sites, which are equipped with centralized resources, staffing capabilities, and subject matter expertise, are far more suited for clinical research involving copious amounts of human intervention and oversight than remote alternatives.

Sponsors also have concerns with preserving data quality when replacing accepted end points and protocols. Apps, electronic patient-reported-outcome (ePRO) tools, and wearable devices require technical and clinical validation – in a revolving regulatory context – to ensure that sensors generate reproducible signals and that signals are relevant to key outcomes. Issues such as device battery life, availability of technical support, and practicality of continuous monitoring with in-home devices and wearable sensors, are factors that necessitate advanced technical, organizational, and human capital capabilities not yet widely present in standard clinical development programs.

Nevertheless, Quadriga Partners believes the increasing prevalence of DCTs is certainly the new normal. Although, where companies will eventually fall on the decentralization spectrum is far less certain.

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Select Tech-Enablement of Pharma Services Transactions

(in millions)

Target	Buyer	Price	Date	Target Description
Pharma Intelligence	Warburg Pincus	2,790	Feb-22	Provider of specialist intelligence, data, and software for clinical trials, drug development, and regulatory compliance catering to global pharma and life sciences analytics markets
REALTIME CLINICAL TRIAL MANAGEMENT SYSTEMS	LLR Partners	NA	Jan-22	Developer of clinical trial management software intended for research sites, site networks, sponsors and contract research organizations (CROs)
GENESIS RESEARCH	GHO CAPITAL	275	Nov-21	Provider of real-world evidence, health economics, and outcomes research data and research solutions to pharma, biotech, and medical device clients
Medable	Blackstone	304	Oct-21	Developer of decentralized trial platform software for clinical trials
greenphire	THOMABRAVO	1,100	Jul-21	Developer of financial management tools, including debit cards, to automate elements of clinical trials
4G CLINICAL	Goldman Sachs	280	Jul-21	Developer of randomization and trial supply management software designed to accelerate clinical research.
MEDISPEND	SUSQUEHANNA GROWTH EQUITY	NA	May-21	Developer of SaaS compliance solutions: Engagement Manager, Transparency Solution, Grants Manager, Study Manager, and Advisory Services for life science companies
Science 37	LIFESCI ACQUISITION II	200	May-21	Developer of decentralized trial platform software for clinical trials
Within3	INSIGHT PARTNERS	100	Sep-20	Operator of a virtual engagement platform intended for healthcare professionals to collaborate with patients.
ActiGraph	ArchiMed	NA	May-20	Developer of physical activity and sleep or wake monitoring device designed to facilitate users to configure and initiate data collection from a mobile device.