A Small CRO's Approach to Global Clinical Trial Execution

PROMETRIKA, LLC

PROMETRIKA
A FULL-SERVICE CRO

WHITEPAPER

Introduction

The globalization of drug development allows companies to more quickly commercialize their product in key markets and reach a wider net of patients. As of August 2023, 64% of the studies posted on ClinicalTrials.gov included a country outside of North America, and each year this number only continues to grow. While globalization certainly offers attractive benefits to most sponsors, these benefits come with many complex challenges to consider before diving in head first. There is a high demand to partner with Contract Research Organizations (CROs) to assist in the planning and execution of global clinical trials.

For small and emerging biotech and pharmaceutical companies, scaling to the global arena can be a daunting concept that comes with considerable risk. Global CROs can often offer the first-hand expertise of running many multi-regional clinical trials (MRCT) across a wide range of indications to help steer sponsors clear of the common pitfalls.

This white paper explores the advantages of partnering with a small global CRO versus a large global CRO when planning a global clinical trial. The paper highlights how the streamlined communications, specialized expertise, quality relationships, advanced technology and processes, and agile workstreams offered by small CROs are an ideal choice for Sponsors looking to successfully execute a complex and geographically diverse clinical trial.

Top Global Challenges Experienced by Sponsors

The coordination and execution of most clinical trials can present challenges. These challenges become exponentially more complex when involving multiple countries. Coordinating research activities across different countries, varying regulatory and local authority requirements, cultures, healthcare systems, and economies, introduces a number of multifaceted considerations for executing a global clinical trial. Examples of the top challenges include:

Diverse Regulatory Requirements

For certain countries, regulatory approvals can take months. Many countries require approval from their health authorities before starting a trial involving human subjects. These complex processes and approval requirements, documentation, and language considerations can slow down trial progress. This can be especially true when your team isn't familiar with the local standards necessary to manage the trial from a different country (Minisman 2012).

Logistics and Supply Chain

As clinical trial protocols and product manufacturing requirements become more complex, supply chain considerations are greatly impacted. Supply chain managers are challenged further when multiple countries need to be considered (Costello and Getz 2012). Many countries have specific import and export regulations and laws that must be followed. Additionally, operational factors such as pharmacy staff experience, storage capabilities, long range shipping, and regional climates and temperatures, all must be addressed in supply management planning.

Language Barriers

As a trial involves multiple countries there are more opportunities for language barriers to arise within the study team as well as between patients and site staff. Language barriers can create risk to the quality of the study and ultimately harm patient rights (Squires 2019). Misinterpretation of the protocol, the consent, or even simple instructions between team members can slow the study down and have significant impacts to study integrity, costs and timelines (Applied Clinical Trials, 2003).

Ethical and Cultural Considerations

During country selection for a clinical trial, it is important for the Sponsor to consider the level of research experience within each country. In recent years, low and middle GDP countries have become attractive to Sponsors to recruit treatment-naïve patients and provide access to healthcare that patients otherwise may not have. However, it is important to ensure the staff conducting the research is qualified and the regulations in place are protecting the patients if considering a country with less research experience (Aguilera 2020).

Data Quality and Integrity

Introducing more than one country on a trial has the potential to introduce variation in the data collection methods and clinical trial practices. This is especially true when less experienced countries are included among the selected countries to participate. Without the proper oversight and centralized monitoring procedures in place, the quality and integrity of the data collected for the study can easily be put at risk.

Time Zone Differences

Clinical trials are fast moving and often information is needed in an expedited manner. Time zone differences can cause delays in communication and decision making. In addition to this, cultural differences with working hours and days, as well as holiday closures, can cause significant timeline delays with milestone planning.

Optimizing Global Trial Execution

As a Sponsor, you don't want unnecessary barriers impeding your progress. That's why it's essential to address the common factors that can contribute to the top challenges outlined above during a project's planning phase. When you're examining whether a potential CRO is the right fit for your unique company and clinical trial, consider a small global CRO with a global strategy designed around five key pillars.

Strong global oversight and deep local expertise	**Tailored approach and a commitment to partnership**	**Streamlined communication**	**Advanced technology and processes**	**Flexibility and agility**

Strong Global Oversight and Deep Local Expertise

For smaller, US-based CROs, forming strategic CRO partnerships with local CROs worldwide, is a well-established strategy to offer global clinical trial capabilities.

An example of a strategic CRO partnership structure may look like the following:

- The US-based CRO remains the centralized project lead and works with existing, trusted partners who live in the region where the trial is being conducted. Local partners provide the resources for activities which cannot be wholly performed by the central US-based CRO (e.g., site management, clinical monitoring, local vendor management, and addressing local regulatory obligations).
- Local experts understand the complex regulatory landscape and are up to date on current submissions and approval requirements, regulations and guidelines, as well as local language requirements, which improves efficiency and accuracy of the trial (Sheetz 2014).
- The local CROs are fully integrated with the US-based CRO for continuity and efficiency. Examples of how this is supported operationally may include:
  - A single set of standard operating procedures (SOPs) are used across the globe by all CRO partner team members.
  - All global team members utilize the same technologies and tools to support the trial (e.g., electronic trial master file (eTMF), clinical trial management system (CTMS), time coding system, learning management system, quality management system, and email system).
- Communication channels are properly structured for the needs of the overarching strategic CRO relationship as well as the project.
  - Global CRO Partner meetings to support strategic planning, innovative initiatives and governance of the work performed.
  - Global Project Team meetings to support knowledge sharing and relationship building.
  - Local Team meetings to support decentralized study execution and agile conduct of the clinical trials.
  - Centralized technologies to support real time data capture and status updates regardless of timezone differences.

The PROMETRIKA Way

Our existing global partnerships span across over 80 countries on five continents (Figure 1). Our partner CROs are similar in size and philosophies, with an average of 15 years in business. As a combined global team, we have over 300 employees worldwide and have conducted thousands of clinical trials.

Our global team meets for quarterly governance meetings to discuss current projects, pipeline opportunities, goals and objectives, and innovative solutions for the future. In addition to this, we meet in person, annually, for a partner summit. The summit is hosted by a different partner each year, allowing us the opportunity to experience the rich and diverse cultures of our group. We also invest in in-person and remote training opportunities for our global team to learn the most up-to-date strategies for successfully planning and executing a global clinical trial. Lastly, there is an established quality assurance structure to support continued auditing across all partners.

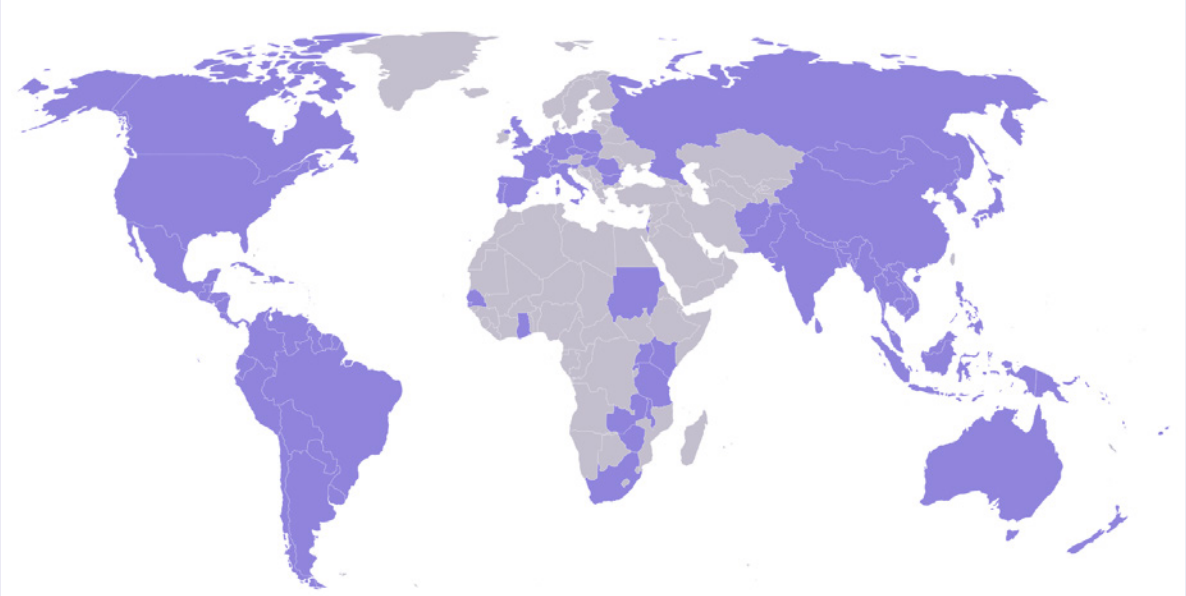

Figure 1: Example of where PROMETRIKA has established strategic global CRO partners

Tailored Approach and a Commitment to Partnership

The way a Sponsor, CRO, third-party vendors, and study sites interact significantly impacts the overall success of a clinical trial and development program. Seamless collaboration between Sponsors and CROs is incredibly important to the quality of the clinical trial, on time completion, and at or under budget delivery (Halloran 2017; Henderson 2013; Moat 2023).

Examples of successful strategies to help build and maintain effective working relationships during a global trial include:

- **Create a culture of community**. It is vital for the global CRO team to maintain a close-knit environment of colleagues who enjoy working together and care about one another. This helps maintain overall responsibility and eliminates miscommunication. It also avoids high turnover, which helps Sponsors have continuity in resources and deliverables from the CRO.
- **Develop site communication opportunities and structured processes**. Most sites relish the opportunity to be involved and offer insights on operational issues that can improve protocol assessments, study start-up, patient recruitment, and data quality. Some methods for obtaining ongoing site feedback include:
  - Using technology (e.g., email, e-questionnaires, surveys) to help provide regular trial updates and seek ongoing feedback.
  - Taking time for face-to-face meetings, which builds and fosters much deeper lasting relationships. These can include:
    - Group meetings with key investigators and site staff.
    - Industry conferences, which create a forum where people can raise issues and find solutions together without taking time away from busy clinic schedules.
- **Involve patients.** Establishing a patient advisory board and feedback loops from the patients to the Sponsor or CRO considers all critical stakeholders in clinical trial effectiveness.

The PROMETRIKA Way

We are united with our global partners in a culture that cares about one another and our commitment to our Sponsors. This allows us to keep our relationships with Sponsors, sites and patients strong even when they are at a global level. Many of our leadership team members have been with PROMETRIKA since its inception. Our executive leadership has regular touchpoints with every project, regardless of its size, ensuring Sponsors get the highest level of expertise and attention. Our Sponsors enjoy this same level of attention when working with our global partners.

Streamlined Communication

Frequent and transparent communication between Sponsor and CRO functional area teams is essential for a successful clinical trial. In studies with a global reach, having a Global Project Manager (GPM) who takes responsibility for the success of the project keeps the project on track. The GPM oversees all functions, and a Global CTM and a Global Regulatory Lead oversee teams of local experts in their respective areas. Examples include:

- The GPM serves as the principle point of contact for the overall project (Figure 2).

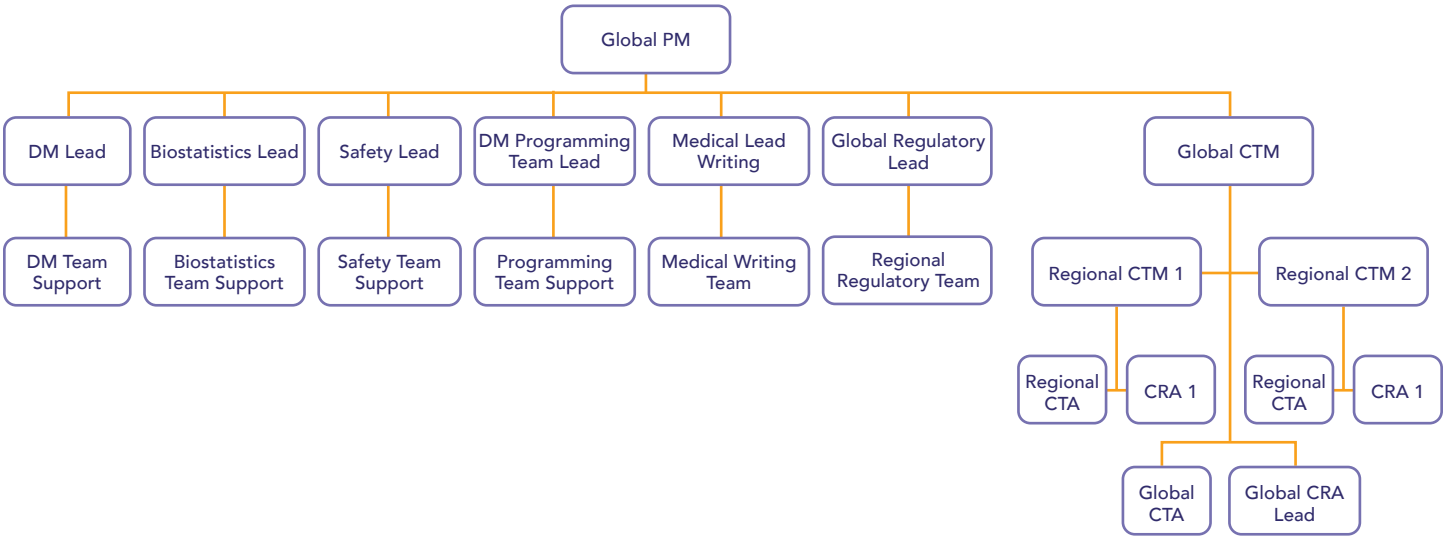

Figure 2

- The Global CTM (GCTM) holds regular meetings with the Regional CTMs to understand country specific status updates, issues and escalations. These discussions translate into consistent methods and messages for regional personnel and vendors to implement. The GCTM communicates this information to the GPM and Sponsor in an organized and structured fashion.
- With current technology, the global team engages in real-time communication regarding the trial's progress. This allows the team to identify areas of concern before they become serious obstacles for efficient, high-quality data collection.
- The GPM keeps Sponsors informed, solicits Sponsor collaboration and decision-making, and is timely, engaged, and responsive.

The PROMETRIKA Way

At PROMETRIKA, we establish project communication plans to ensure streamlined communications. In addition to this, we consider the needs of the Sponsor and adapt our plans to ensure the right information gets to the right Sponsor stakeholders at the right time. This often includes updating our project status reports to align with the preferred Sponsor format or setting up custom Sponsor dashboards with clear preferred metrics and information. We allow our Sponsors full access to our clinical tools, including the CTMS, to support having the ability to retrieve real-time information around the clock. Our goal is to ensure the success of the project; transparent communication is critical in this endeavor.

Advanced Technology and Processes

Using the most advanced technology and processes helps create an integrated data solution for each clinical trial, with a goal of ensuring data are as cohesive and streamlined as possible for analyses and submissions to regulatory agencies.

Through recent technological advances and decentralized processes (e.g., wearable devices, electronic data capture, remote monitoring capabilities, telehealth, traveling nurses), Sponsors get a real-time view of trial data, increasing surveillance of subject safety and data integrity. There is often a notable decrease to patient burden. These technologies lend themselves to **central monitoring**, which leads to more efficient data surveillance and reduced onsite monitoring costs.

Worldwide regulators like the US Food and Drug Administration (FDA) are encouraging greater use of centralized monitoring practices, where appropriate, to fulfill the responsibilities of monitoring (US FDA 2019). Using the right technology and customized monitoring techniques, centralized monitoring can effectively identify and mitigate:

- High-risk clinical sites – sites with a higher frequency of data entry errors, protocol deviations, or data irregularities
- Efficacy and safety data trending, such as (serious) adverse event distribution and outliers
- Data quality issues, which may compromise the study results

Sponsors looking for CRO partners should search for CROs with experience in flexible monitoring models and technology that allows for real-time data review methods.

Central Monitoring

A remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted.

The PROMETRIKA Way

At PROMETRIKA, we enhance our experience and skills with the support of the top EDC, CTMS, eTMF, eCOA, IWRS, data analytics, smart technologies, and project management platforms. Our project teams utilize the same systems on each project across the globe, allowing our Sponsor access to a unified platform to see the complete global status of the study at any given time.

Our global teams are continually trained on new functionality and reporting capabilities to deliver clear, well-organized metrics to Sponsors. We continually assess ways in which our technology can improve. Our agile business methods allow us to quickly adopt next-generation technologies as they become available and provide a customized technology strategy based on the Sponsor's vision.

Flexibility and Agility

Sponsors' needs often shift, depending on many different expected and, at times, unexpected events – especially as they advance through the clinical trial process and expand globally. For a successful trial, CROs must be flexible and agile in the delivery of the trial, adjusting workstreams as quickly as needed to meet short turnaround times. Sponsors should engage with CROs who have proven they can adapt to changing needs. Flexibility is often hand in hand with strong communication and technology, which supports the swift roll-out of clear, updated priorities and needs of the trial.

The PROMETRIKA Way

Our size allows us to be competitive and efficient in meeting time-sensitive budgetary restrictions without sacrificing the quality of deliverables. We also understand that working globally could require the need for new technologies and communication pathways to support countries that may not traditionally have been considered for participation in clinical studies. Our flexible global business model allows us to adopt new operational tools quickly and effectively. Each of our Sponsors' experiences are tailored to their specific needs.

Conclusion

As Sponsors continue to expand clinical trials globally, partnering with a CRO with a model that includes these five key pillars reduces some of the most common challenges that extend trial timelines and costs. Small CROs are more likely to save Sponsors time, money, and human resources as they complete clinical trials across the globe than the larger CROs, burdened by silos, high turnover and complex processes. Small CROs accomplish this through streamlined communication, local and global expertise, quality relationships, advanced technology and processes, and agile workstreams.

About PROMETRIKA

PROMETRIKA, LLC is a global, full-service clinical research organization (CRO) supporting the biopharmaceutical and medical device industries since 2003. Based in Cambridge, Massachusetts, a biopharmaceutical hub, PROMETRIKA has provided over 20 years of experienced, professional support to local, national, and international clients. Our proximity to New England's thriving biotechnology research environment has enabled us to establish strong, collaborative relationships with companies developing some of the most innovative and promising new therapies available. We offer full services in clinical operations, data management, biostatistics and programming, medical writing, pharmacovigilance, and regulatory submissions.

Please contact Chris Gallant at cgallant@prometrika.com to connect with one of our clinical development experts.

About AICROS

AICROS, the Association of International CROs, is an official network of small to midsize CROs with a proven track record of more than 10 years' experience providing clinical research services for the pharmaceutical, biotechnology, and medical technology industries. With the experience gained throughout the years, AICROS colleagues know the challenges the sponsor faces in every step of the clinical development process. Through the specific strengths of our respective member organizations, we overcome development constraints by quickly adapting to changing environments, adhering to specific client requirements, and applying proactive problem-solving approaches throughout the whole project

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