CASE STUDY: **BRINGING A 10,000-PATIENT CARDIOVASCULAR OUTCOME TRIAL TO DATABASE LOCK**

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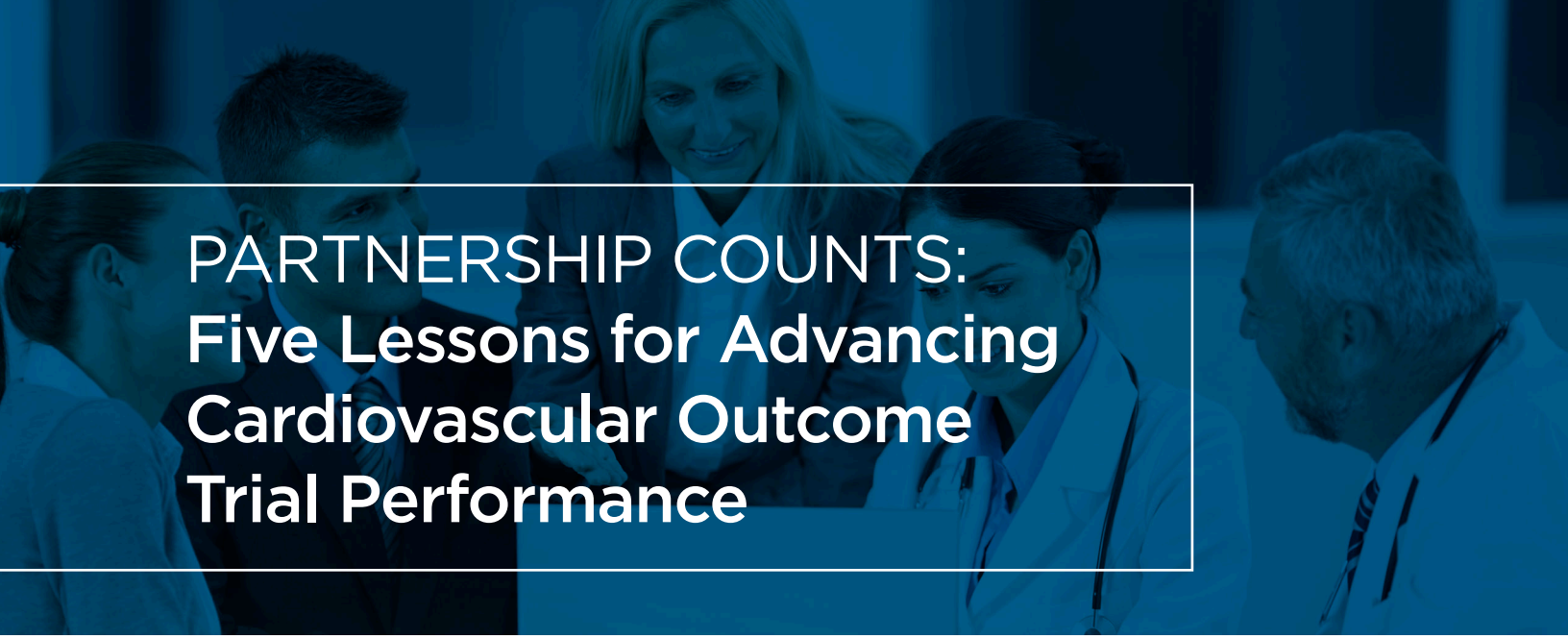


PARTNERSHIP COUNTS: **Five Lessons for Advancing Cardiovascular Outcome Trial Performance**

Relationships often dictate the value of clinical trial outsourcing projects. Sponsor success or failure depends on how well partners perform, and good relationships deliver better results.[1]

This is the story of how three parties – Worldwide Clinical Trials, the sponsor, and an academic research organization (ARO) – formed a strategic partnership that extended to key opinion leaders and third-party providers. The highly collaborative approach guided a large cardiovascular outcome trial (CVOT) toward achievement of recruitment and study milestones ahead of plan and offered five valuable lessons for avoiding heartbreak while managing these mega-projects.

Mega trial: 10,000 patients at 500 clinical sites in 12 countries

Cardiovascular outcome trials are post-approval studies mandated by the FDA in 2008 and by the EMA in 2012 for new antidiabetic therapies that fail to meet a certain threshold of cardiovascular risk.[2,3] More recently, they have been introduced for anti-obesity drugs and other therapies with the potential to increase cardiac events.

Worldwide puts a priority on ensuring the mandates are fulfilled but also recommends these trials serve as the foundation for compiling other measures and outcomes data that are of interest to non-regulatory stakeholders. Worldwide Evidence™ is a dedicated unit within the company designed to help clients improve the value of CVOTs in documenting other clinical, economic, and humanistic outcomes of interest.

In this case, Worldwide was engaged to enroll approximately 10,000 patients at nearly 500 clinical sites in 12 countries. As the numbers suggest, these large outcome studies are substantially different than typical registration trials, with more moving parts, people, and clinical sites – a combination that makes them tricky at best.

Large quantities of data: 1.5 million case-report-form pages and 1.2 million queries

To manage this CVOT, Worldwide enlisted experts in global project management, clinical monitoring, data management, regulatory affairs, vendor management, bio-statistics, translations, and site contracts. This intent-to-treat study took 20 months to enroll and achieved an enrollment rate of approximately 1.5 patients per site per month. The follow-up took 2.5 years after randomization and included 10,000 site monitoring visits. Recruitment and study milestones were achieved ahead of plan.

Read on to learn the details of this remarkable partnership and the 5 lessons for clinical research collaboration that can be applied to future clinical trials.

1 Partnership Is More Than a Contract

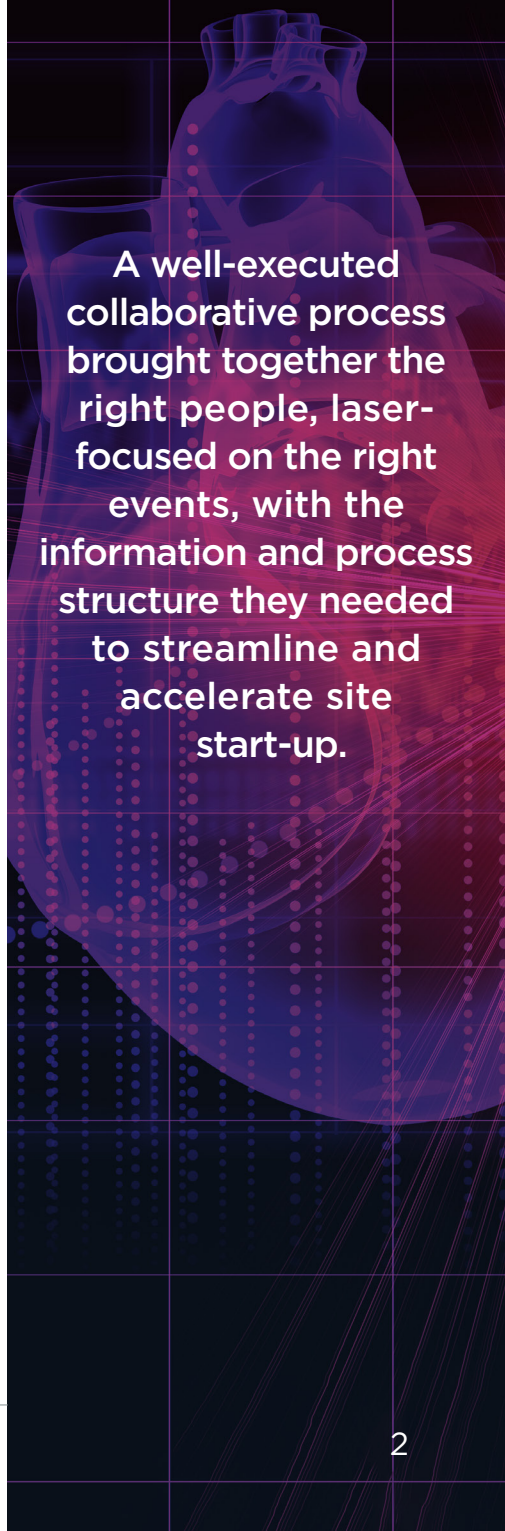
In this CVOT, one of the largest issues arose when a major protocol change was required. A new endpoint had to be added to satisfy the revised protocol. Producing an approved protocol revision was expected to create substantial delays in getting clinical sites started with the trial. Apart from the procedural headaches, defining the new endpoint proved challenging due to the variable methods of diagnosis across the many regions in the study.

The team addressed this issue by establishing a clearly defined event adjudication process. The adjudication team consisted of physicians from the sponsor, Worldwide Clinical Trials, and the ARO, which has collaborated with Worldwide as a partner in past studies. The doctors, many of them key opinion leaders affiliated with the ARO, would approve or disapprove each event according to the updated study protocol.

A good working partnership was essential to the new adjudication process. Worldwide Clinical Trials was not a preferred provider in this case. But the sponsor made the decision to treat Worldwide and the ARO as true strategic partners, and it made all the difference.

Worldwide is known for taking an uncommon approach to collaborating with sponsors and other partners. The sponsor responded favorably to Worldwide's past relationship with the ARO and chose to cultivate the spirit of partnership without a contractual obligation. From the start, Worldwide established regular meetings with consistent communications and well-defined roles and responsibilities.

As a result, site start-up was streamlined and accelerated. The collaboration resulting from this key sponsor decision proves that true partnership is more than just a contract.



A well-executed collaborative process brought together the right people, laser-focused on the right events, with the information and process structure they needed to streamline and accelerate site start-up.

2 Maximize Partnerships to Manage Third Parties

When designing this cardiovascular outcome trial, Worldwide introduced an electronic trial master file and converted most processes to fit the system requirements. However, one part of this conversion did not go well.

The sponsor had contracted with a technology vendor to support clinical site activation and drug shipments. Originally designed to handle transactions for 30 clinical sites, the system failed when attempting to manage activities for 500 sites, putting site initiation and drug distribution on hold.

In response, Worldwide worked with the sponsor, ARO, and technology vendor to clearly outline the scalability needed to support a study of this size. In the end, the teams were able to leverage relationships with a central institutional review board, accessing its 20 sites to pilot a system upgrade and expanding the rollout to the remaining sites. Thanks to open dialogue and proactive collaboration, the system went from initiating a few sites every week in its original configuration to initiating hundreds of sites at once.

An additional benefit to getting site initiation back on track was increased confidence among site staff. They reported that the proactive approach to improving the system convinced them that if other issues came up during the study, the partners would work together again to quickly implement solutions.

Out-of-the-box thinking led the team to scale from initiating a few sites every week to initiating hundreds of sites at once.

3 Implement Proactive Strategies Such as Pre-screening

The study faced another challenge when the sponsor had to withdraw it from several countries due to regulatory issues. As a result, a large number of the clinical sites had to be withdrawn, including those that had made considerable progress toward initiation. The change was expected to delay the program by several months.

Worldwide managed the change in three distinct and uncommonly effective ways.

1. Used a broad feasibility analysis to identify backup sites. Most feasibility studies focus only on sites that would qualify given the initial protocol. But Worldwide looked more broadly to qualify other sites in case circumstances changed.
2. Suspended enrollment at fast-enrolling sites so slower enrolling ones in newly added countries could add participants.
3. Asked clinical sites to identify the number of patients they would likely enroll if activated. This pre-screening process helped to clarify site potential before recruitment started.

Approved by the sponsor and ARO, these three steps accelerated enrollment sufficiently to meet the initial targets despite the months of delay that had been forecasted.

The lesson here is to have a broad feasibility analysis that identifies countries well-suited for the patient population and for the study, and then having a backup plan so that if there are unanticipated regulatory questions the study is well-positioned to bring on new countries and additional sites.

When it comes to contingency planning, the old adage of "plan for success, prepare for adversity," cannot be overstated. Despite the months of delay that had been forecasted, Worldwide met initial enrollment targets.

4 Patient Retention Begins Before Study Launch

Worldwide's proactive approach – evident in how timelines were met even after the countries withdrew – guided the study in many other ways.

As noted, CVOTs are a long-term proposition driven by the number of events recorded. Every patient is included and all data are analyzed – whether patients stay in the study or not. However, over the course of an outcomes trial, some participants inevitably get tired of participating. Those who drop out and cannot be found are considered lost to follow-up. The US Food and Drug Administration and other health authorities classify patients as deceased if they are lost to follow-up. And a lost to follow-up ratio higher than 2% can affect FDA approvals.

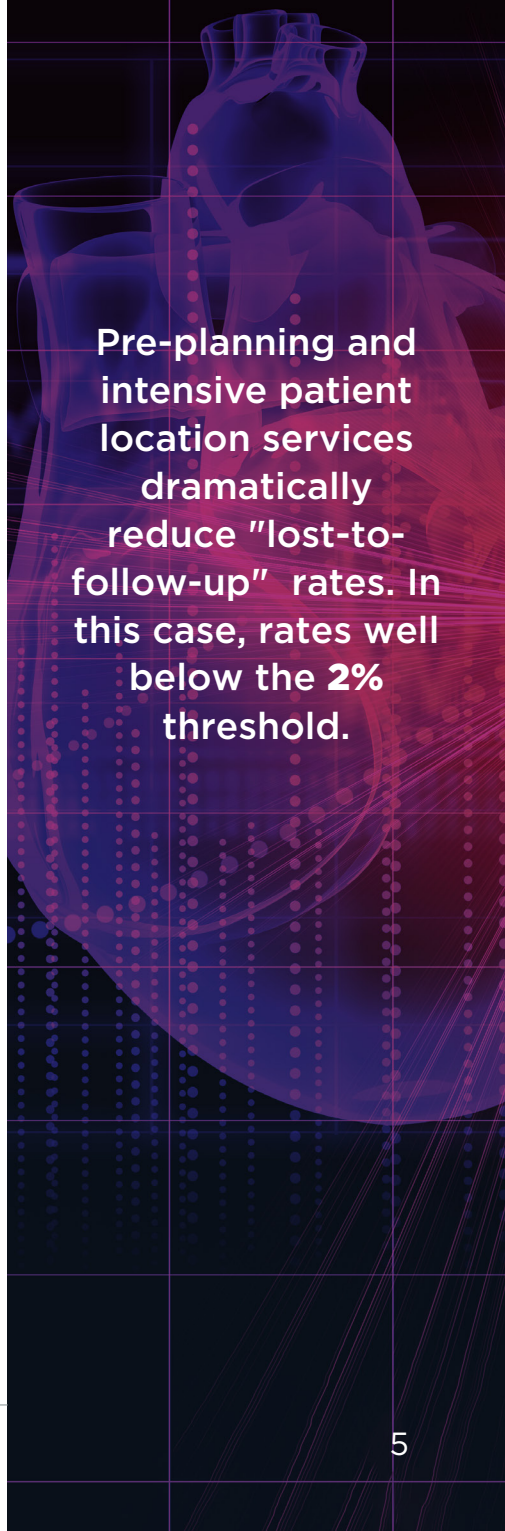
Traditionally, site coordinators are tasked with chasing these "lost" patients if they fail to show up for clinic visits. This approach has limited success. Instead of following tradition, Worldwide thought outside the box to identify and support patients at risk of dropping out.

Obtain contingency contacts during informed consent

After receiving partner approval, the informed consent documents were updated to ensure consistent patient communications throughout the trial. Participants provided a list of contingency contacts in case their primary contacts were unavailable. The list could include employers, neighbors, friends, or extended family. The new form made it clear how critical it was to know patient status for the duration of the clinical study. Worldwide then worked with the sites to identify potential dropouts, such as those who missed visits or went off drug for no medical reason.

If unable to reach participants using their expanded contact list, Worldwide employed a patient finder service. This service is authorized to conduct public database searches, home visits to determine current address, and other intensive location activities. The patient finder service helped Worldwide keep the lost to follow-up rate well below the 2% threshold.

The bottom line is that patient retention begins before clinical studies actually start.



Pre-planning and intensive patient location services dramatically reduce "lost-to-follow-up" rates. In this case, rates well below the 2% threshold.

5 Escalation Path Paves Way to Database Lock

In a long-term clinical trial, such as a CVOT, it can be helpful to understand study conduct by taking short-term snapshots. For example, Worldwide's data management team faced the challenge of entering 9,400 patient visits over a three-month period while ensuring the data were clean.

There were four keys to managing the data.

1. A fit-for-purpose database using dynamic workflows,
2. A robust reporting module,
3. Pre-defined cleaning milestones to prepare for the closeout period, and
4. Robust communication and escalation paths.

The project included comprehensive training for the sites and study team. Worldwide held initial meetings to explain the types of data required, as well as review documentation and update procedures.

Setting pre-defined cleaning milestones prepared staff for closeout. Once subjects completed visits one through five, Worldwide data team leaders set a target date to have those visits cleaned and locked. Then, staff performed cleaning sweeps to check and review the data.

To collaborate with the clinical team, Worldwide implemented a closeout reporting tool. This helped prioritize and track all subject visits and provide updates on data entry and subject follow-up status. That way the entire study team was well aware of where subjects were in the study at all times.

Unresponsive Sites Enter Escalation Path

Next, a robust site escalation plan was developed with the sponsor and the ARO to ensure data were entered and queries resolved on time.

Using this plan, Worldwide staff identified sites that were unresponsive to queries. Site personnel had a certain time period to respond before their clinical research associate (CRA) would contact them. If there was still no response, Worldwide staff had several escalation levels in place before involving project management and ultimately the sponsor and the ARO.

The CRAs would also follow up frequently with the sites to answer any questions. Those that the CRAs were unable to answer would be escalated through the questions path until they were resolved.

All these strategies, combined with a full-team effort, resulted in on-time database lock, as well as on-time regulatory filing and publications!

WHAT WORKED?

- **A sponsor's desire to partner at the highest levels.**
- **An uncommon approach to collaboration and innovative thinking.**
- **Full-team planning and preparation.**

UNCOMMON RESULTS

Sponsor initiative, combined with an uncommon spirit of partnership, led to:

- Quality data for **9,400** patients in three months
- **On-time** database lock, regulatory filing, and publications
- Five valuable lessons to **advance cardiovascular outcome trial performance**

ASK THE EXPERTS

Take the next steps in planning your CVOT or other cardiometabolic clinical trial. Please connect with the authors listed below for questions about this case study or your individual research concerns.

Ask Me A Question

KAREN HILL

SVP, Global Therapeutic Leader, Cardiometabolic

Karen joined Worldwide in 1993 and is responsible for Global Project Management within the Cardiometabolic and Late Phase division. She has more than 22 years of experience in the CRO industry and has worked on numerous large cardiovascular outcome studies. In 2003, Karen became head of Project Management, managing and supervising project managers, CRAs, and the IVRS teams. Karen currently heads the Global Cardiometabolic Project Management division and continues to supervise a global team working on large cardiovascular outcome studies, as well as phase II-IV studies in other cardiovascular indications.

Ask Me A Question

NANCY NEWARK

Executive Director, Project Management, Cardiometabolic

Nancy joined Worldwide in July 2010 and has provided operational oversight and leadership for numerous cardiovascular projects. She currently serves as a franchise lead within the cardiometabolic therapeutic area. Prior to joining Worldwide, Nancy worked at Duke University Medical Center for 25 years. She was a critical care transport nurse for the helicopter and ground ambulance program and provided senior operational leadership for global multi-center clinical trials and registries. She had direct responsibility for regulatory compliance, strategic development of project management, site management, and clinical monitoring at the Duke Clinical Research Institute.

Ask Me A Question

CHRISTIE KOPPENHAVER

Program Clinical Data Manager, Worldwide Clinical Trials

Christie has worked in clinical research for more than 13 years and joined Worldwide Clinical Trials in November 2016. She began her research career in Data Management as a nurse-reviewer of clinical data. Christie then worked as a Lead Data Manager for several years before joining an EDC provider. Christie learned firsthand how databases are built from the ground up, working with clients globally. She returned to Data Management as a lead, overseeing activities from kickoff through database lock. Christie has worked across all phases of research in various therapeutic areas, specifically cardiology and oncology.

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