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THE CONSOLIDATION AND REINVENTION OF CLINICAL RESEARCH SITES

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TRENDS IN THE SITE CONSOLIDATION LANDSCAPE

In recent years, institutional and private investors have made significant investments in the research site space. Some are consolidating free-standing research sites into a single network, while others are partnering with health systems through an outsourced research model.

This booklet consolidates a series of interviews with leading strategists. They express a range of perspectives and strategies. However, they agree on one theme: clinical research site operations are undergoing a necessary and long-term transformation towards professionalization and scale.

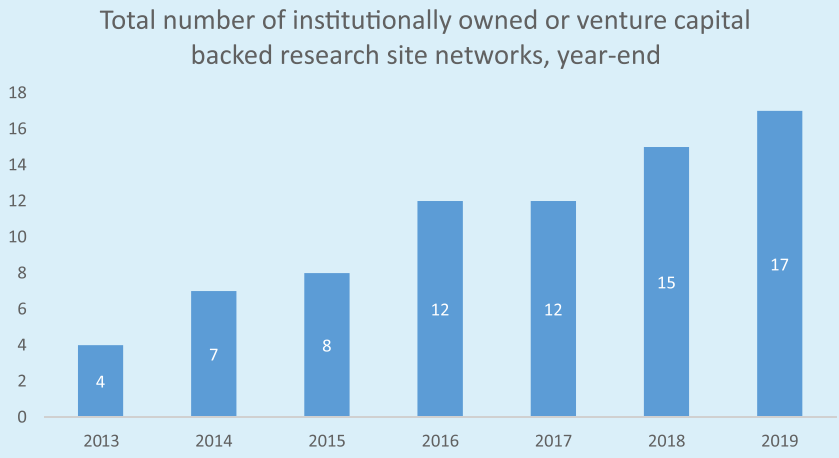
At Clinical Research IO, we are developing the next-generation technology platform to power clinical trials in this environment. We hope this booklet deepens your understanding of industry trends and helps inform your business strategy.

Regards,

Raymond Nomizu

Co-founder, Clinical Research IO

Institutional investors in clinical research sites



Source: Web searches; used original institutional investment date
Contact info@clinicalresearch.io for back-up information

SITE NETWORK AND SMO CONSOLIDATION: THE FUTURE OF CLINICAL RESEARCH

Mr. Blume is a Co-Founder and Managing Director of Edgemont Partners and has over 30 years of investment banking experience, including more than 25 years representing healthcare companies in M&A and capital raising transactions. He has completed over 150 transactions, representing more than $60 billion in value. He has provided strategic advice and raised capital for pharmaceutical research and development services companies such as CROs, clinical sites and networks, and other pharma services companies. David has closed over 25 M&A transactions for clinical research site companies. He graduated from Haverford College with a Bachelor of Arts in Philosophy in 1988.

Clinical research sites have historically been a highly fragmented industry, consisting mostly of physician practices conducting studies on a part-time basis and small stand-alone businesses. Now, consolidation is occurring, with sites coming together under common ownership, or management, to operate as a single network at an unprecedented rate.

The value proposition of a single network includes:

- Geographic and therapeutic diversification through multiple locations and PIs
- Economies of scale from centralizing functions such as business development, budgeting, contracting, study start up, finance and accounting, QA and IT
- Standardization of workflows and processes around best in class SOPs
- Enhanced negotiating leverage with sponsors through the ability to offer volume, accelerated timelines, and data consistency

BASICS OF THE CLINICAL RESEARCH INDUSTRY

Before we talk about the consolidation trend between clinical trial sites, it is important to distinguish between two business models in the clinical research industry:

1. Free-standing research sites or dedicated research centers:
These sites only perform research and do not provide ongoing clinical care (outside of the study duration). They have a dedicated facility, hire physicians as employees or contractors to serve as principal investigators, and source their patients from advertising, their subject database, partnership with health care providers, and community outreach. The advantages enjoyed by these free-standing clinical trial sites are focus and greater ability to control operations, but they generally require more capital and operate at higher break-even thresholds.

2. Physician affiliated:
These sites are co-located within physician practices and manage research on behalf of those practices. They use the physician's facility, source patients primarily from the practice database, and share revenue with the physician. This arrangement is more subject to the whims of the practice, but is easier to scale, with lower break-even thresholds.

A site network is simply a combination of sites pursuing one or both of the above models. Some networks are exclusively free-standing; some are exclusively managed (SMO); and some combine both types under one operation. For instance, a local network might resemble a hub-and-spoke, with a large stand-alone site (the hub) that sends coordinators over to neighboring physician practices to manage operations (the spokes).

THE RISE OF PRIVATE EQUITY IN CLINICAL TRIAL SITES

Private equity and other institutional investors have shown increased interest in the space. For private equity firms, the investment thesis is straightforward: An opportunity to consolidate operations in a highly fragmented industry, creating a predictable cash-flow business with economies of scale.

Many are actively pursuing freestanding sites in a roll-up strategy. When acquiring sites, firms like to buy operations with a minimum revenue size ($2 mm is common), a track record of predictable positive EBITDA (Earnings Before Interest, Taxes, Depreciation, and Amortization), and a diversified PI base, or, at minimum, an active PI who agrees to stay on for an extended duration.

Because of increased buyer competition, large, well run sites often receive multiple overtures. One private equity investor tells us that EBITDA multiples are now in the 5-7x range for research sites with more than $1.0mm of EBTIDA and 8+x EBITDA for sites with over $3mm in EBITDA (where EBITDA includes the expense of market rate compensation for the PIs/owners). For instance, a site with $3.0 mm in revenue might generate $1.0mm in EBITDA (which is a 33% EBITDA margin) and therefore command a purchase price of $5.0-$7.0 million.

Other institutional-backed companies are pursuing a purely physician-affiliated strategy. To scale, these companies are pursuing alliances with a large volume of physician practices. Large health systems are especially attractive partners because of their size and reach, both in the pool of PI's and patients.

"One private equity investor tells us that EBITDA. multiples are now in the 5-7x range for research sites with more than $1.0mm of EBTIDA and 8+x EBITDA for sites with over $3mm in EBITDA"

TAKE A LOOK AT THIS TABLE OF SITE NETWORKS BACKED BY INSTITUTIONAL INVESTORS:

NETWORK	OWNER/INVESTOR
AMR LLC	Individual Site Owners
eStudy Sites	Celerity Partners
Velocity	NaviMed
Vitalink (fka ABR)	Great Point Partners
Meridien	Avego Healthcare Capital
BioClinica	Cinven
AltaScience	Audax
ERG	Linden Capital Partners
JBR Clinical Research	Webster Capital
Synexus	Jaguar Holding Company
PMG	Icon
Wake Research Associates	M3 Inc.
Circuit Clinical	Venture Capital
Q Care	IQVIA
Elligo	Venture Capital
Source: Press Releases And Website Disclosures.	

WHAT DOES THIS MEAN FOR THE CLINICAL TRIAL INDUSTRY?

In the long term, active consolidation should raise the level of professionalism in the industry. It should create more standardized operations, less variability in performance across sites and, ultimately, more predictability for sponsors in terms of trial enrollment and data delivery.

It could improve enrollment for the industry significantly by allowing sponsors to tap research-naïve physicians with access to specific patient populations. Imagine a physician who has a patient population that fits a particular study, but does not have the experience or infrastructure to run research. With the rise of network operators, this physician can partner with an operator to perform clinical research. For a sponsor, this partnership combines the benefits of patient access with best-in-class operational know-how.

All of this will lead to more adoption of site technology. Already, the vast majority of site networks have a CTMS system to manage back-office operations, and now, many are adopting eSource and eRegulatory as a means of driving standardization and enabling centralization of more functions. For example, instead of simply centralizing business development, finance and QA, a network can also centralize regulatory compliance, source design, and EDC entry with the use of these tools.

Significantly, several of the start-ups targeting larger health systems have made the explicit decision to go with eSource as opposed to using the health systems' Electronic Health Record system so they can have better operational control. This means that the direction of the industry will be toward industry-customized data collection platforms as opposed to EHR systems which are optimized for patient care.

Given the pace of change in the industry, site consolidation could take years to fully play itself out. But this should lead the way towards superior operational performance and an expanded pool of research-ready Principal Investigators.

"Several of the start-ups targeting larger health systems have made the explicit decision to go with eSource."

HOW I BUILT AND SOLD THE WORLD'S LARGEST LATE-PHASE CLINICAL RESEARCH SITE

Sean Stanton was a principal at CNS Healthcare and then co-founded Compass, a Florida-based site network specializing in Internal Medicine, CNS and Psychiatry. In 2016, Compass had reached 250 employees, and Sean and his team sold it to BioClinica, where he later served as Chief Operations Officer of Site Operations. Sean is currently consulting in the life sciences industry.

HOW DID YOU GET INTO RESEARCH?

I got started in clinical research as an undergrad. There was a group of physicians from Harvard that came to the University of Cincinnati, where I was studying, who started a centralized research office. I was part of that team. The first two years I coordinated, and my last year I learned all about contracts, budgets, etc. Then I hit the trade shows and learned how to interact with pharma companies.

I left school with one of the fellows and we started Psychiatric Institute of Florida, which ultimately became CNS Healthcare, now a major CNS network. This was 1998. It took us almost ten years, and we built that into a series of four mid-sized sites. Each site had roughly 15 people – seven coordinators, a regulatory specialist, a recruiter, a QA director, a site director, a few doctors, and an office manager. We fine-tuned the metrics and ran this network as efficiently as possible.

SO HOW AND WHY DID YOU START COMPASS?

I wanted to pursue a different vision. First, I wanted to pursue multiple therapies, instead of limiting myself just to Psychiatry. Second, instead of building out several sites of the same size, I had a hypothesis that we could build a much larger site at a single location. So I really wanted to push the boundary and see how much further I could grow a single location. I had just had twins and couldn't travel as much, so this dovetailed with that. So, in 2006, my partner Craig Curtis, MD, and I started Compass Research. Craig was an ER doctor with ten years of clinical trial experience and started off as the PI and Medical Director. Because of his training, we could apply for a wide range of study types. Our first areas of focus were in Pain and Internal Medicine. We quickly became the pre-eminent site for fibromyalgia and post herpetic neuralgia. I've always believed that you have to build your center around the physician, not the operations.

> *"I've always believed that you have to build your center around the physician, not the operations."*

HOW DID YOU GROW?

Soon after starting, we brought on other doctors and cultivated them as employee-investigators. We made them PI's early on so we wouldn't be too concentrated in one person. Because of my rolodex from CNS Healthcare, I was able to assemble the talent upfront pretty quickly.

From there, we built up three separate areas: Pain, Internal Medicine, and CNS. We created virtual teams within each area, so we operated as if we were three sites in one. At first, the doctors covered each other across areas, but soon each area became large enough that they could field their clinical teams. We shared the administrative functions across the three teams. So we centralized the management team, the finance, the G&A – we operated like an SMO, with the clinical teams operating separately, only in one geographic location instead of three.

At the five year mark, we opened our Phase I clinic. What happened was the industry started doing more early stage adaptive designs, which meant that now instead of just requiring healthy volunteers, they wanted special populations – people with target indications they could test early on. Since we had these populations, we could leverage them for this work. Right around this time, there was a nearby phase 1 site which had a lot of employees who were leaving. They approached us, so we grabbed them.

THIS ALL MAKES SENSE. BUT STILL, YOU WERE OUT-OF-THE-PARK SUCCESSFUL. WHAT DO YOU THINK WAS YOUR SECRET SAUCE?

First off, a big part of our success was having a growth mentality. Most sites get to four to five coordinators and stop because they are limited by space and/or management capacity. We broke that mold and said "let's see how big we can take this". We kept pushing and pushing, and as we grew we found that there was no natural rate-limiting factor on our growth. Even at the time we sold in 2016, I firmly believed we could have grown to double our size.

One of the keys was bringing on a professional management team. After three years, we realized we had to diversify our team, and bring in people who were smarter than us. Jeff Pohlig joined our team in 2009; he brought very strong operational leadership to complement my visionary style.

> *"We realized we had to diversify our team, and bring in people who were smarter than us."*

That shot us up ten rungs. We also hired a good CFO to help with strategic planning. The CFO helped us with planning and forecasting, allowing us to pilot new initiatives and pivot quickly.

We were able to make breakthroughs on recruiting for Alzheimer's trials. We found a way to network with neurologists locally and in the community. We partnered with non-profit organizations; for instance, the top neurologist in Alzheimer's care, Dr. Goodman, was at a hospital. The hospital decided to disinvest in this type of treatment, so we acquired his practice. We became a healthcare provider, and that tie-in fueled a lot of our research growth. Everyone knew who Dr. Goodman was, so we were able to forge partnerships with community organizations.

We built a satellite facility in The Villages, which was the country's largest 55 and over community, with 120,000 residents. For two years I networked with the ownership of that community and we reached an agreement that we would become the single provider of clinical trials inside that city. We ultimately built out two separate facilities; together, they are the size of six to eight clinical trial sites. In our peak year, we randomized 225 patients across our Alzheimer's portfolio, which was by far the largest enrollment figure in the country.

HOW DID YOU INTEGRATE CARE AND RESEARCH?

We partnered with physicians who had patients who could benefit from clinical trials. We specifically looked for physicians who were motivated to help their patients because it was the right thing to do from a care perspective. In fact, if we sensed that the physician only wanted to do research for the money, we cut off negotiations. Once we knew that our physician partners were appropriately aligned, we could then provide the support and reimbursement for chart review. If the doctor's staff was too busy to do chart review, we would send in our resource to do it.

TWO COMMON CONSTRAINTS ON THE ABILITY TO GROW ARE STAFFING AND REAL ESTATE. HOW DID YOU ADDRESS THOSE?

On staffing, we had a reputation as an attractive place to work, so we were able to have a steady stream of recruits ready. Early on, we created the Research Assistant role, which we staffed at a ratio of one RA to two CRC's. These RA's were our future coordinator team. So we always ensured we had a pipeline of talent. For the real estate, we rented space in a multi-tenant medical office complex. We started with 1200 square feet. We took very low salaries so we could build up cash reserves in the company. As we grew, we worked with the landlord to move into adjacent spaces. At times, when we were too constrained, we would send a coordinator into one of the physician's offices and pay a sublet fee.

"Back in the day, people were rolling up sites as a commodity instead of taking it from a strategic perspective."

What helped with real estate acquisition was having a professional finance team. They could run projections and forecasts, and work with lenders and landlords to identify, acquire and build out space on a timeline that supported our growth.

HOW DID YOU MAKE THE DECISION TO SELL?

I would always attend Wall Street discussion forums to see which therapeutic indications were receiving funding. At one of these conferences, I met David Blume, an investment adviser in the space. He and I became friends. He suggested I valuate the business. So we retained him and he performed an outside-in valuation. It was extremely valuable, and opened our eyes to the possibility of a sale. We decided to market our site network to see what we could get. Ultimately, 32 acquirers expressed interest. So, this started out more as an educational foray, and became an opportunity. We ultimately sold in 2016.

"You should be e-everything. You should find best-in-class vendors and partner with them."

TELL US ABOUT THE CURRENT WAVE OF SITE CONSOLIDATION. WHEN DO YOU THINK IT STARTED, AND HOW IS IT DIFFERENT FROM THE EARLIER WAVE?

I'd say this wave started in earnest around 2010. I was around in the SMO consolidation heyday from the 1990's My opinion is that back in the day, people were rolling up sites as a commodity instead of taking it from a strategic perspective.

Consolidators grew too fast, took on too much, so they failed. Half of the people who sold their sites bought them back for nothing and re-built it. So I think the weakness in many of these models was that there was no solid operational perspective. No one had the perspective, "How can we change the game?" It's so hard to consolidate the space b/c we're a service industry. The sites are small, boutique, often operating under the personality of a single person or group of people. There's not a lot of solid sites out there that are large and institutionalized enough to acquire. However, as an industry, we have to work together and become more professional. If consolidation doesn't work, then we need to consider investing greenfield. In fact, I'm a strong believer in the hub-and-spoke model, where an existing site serves as the hub, and partners with area physicians on a greenfield approach.

AND WHAT ABOUT TECHNOLOGY? DO YOU THINK SITE CONSOLIDATORS SHOULD GO ELECTRONIC?

You have to. And I don't mean just CTMS, but eSource and eRegulatory. You should be e-everything. You should find best-in-class vendors and partner with them. Have them work together.

Right as I was leaving Compass, our team did an ROI analysis for adopting eSource, and concluded we could get a 4x return. We saw huge gains from standardizing operations, cutting down on deviations, saving coordinator time, and centralizing tasks such as EDC entry. This gets to what I was saying earlier about how if you're going to acquire a bunch of sites, you need a strategic perspective to create synergy. You shouldn't just cobble together disparate operations, with different cultures, and have them continue to do things, on the assumption that if you acquire 1, 1 and 1 of EBITDA, it'll magically become 4. You have to identify ways to create a cohesive operating strategy, and technology is one of the elements of that.

WHAT ARE SOME OF THE OTHER ELEMENTS?

Investing in new ways to identify and recruit patients. Complementing hubs with greenfield spokes. Creating a strategic pipeline of studies, where you align your capabilities with areas of future therapeutic growth. Ensuring that you have sites that share the same culture, so standardizing operations becomes easier.

> *"Our team did an ROI analysis for adopting eSource, and concluded we could get a 4x return."*

SELLING MY RESEARCH SITES

Dr. James Greenwald was founder and CEO of Medex Healthcare Research, a three site network with locations in New York City, Chicago and St. Louis. In 2018, he sold his network to a multi-clinic Group, where he now serves as Director of Research. Dr. Greenwald previously served as Medical Director of a network of medical testing sites and Assistant Professor at Washington University School of Medicine. He has an MD and PhD from Ohio State University and did his residency at Johns Hopkins.

TELL US ABOUT HOW YOU BUILT UP YOUR SITE NETWORK.

I started Medex Healthcare Research in 2001, originally in St. Louis. At the time, I owned and ran some medical clinics that performed disability examinations for the social security administration. Since these facilities employed physicians and psychologists, we felt we had the framework of providing clinical trial management to the pharmaceutical industry.

After building the St. Louis site, I relocated to New York City. Where I opened the NYC site. With our location and access to millions of people, we became a high enrolling site. We built up a database of over 40,000 patients. Later, we opened a site in Chicago. I served as Principal Investigator at the NYC site, and CEO and Medical Director of the overall network.

AND YOU WERE ELECTRONIC FAIRLY EARLY ON, RIGHT?

I actually moved to electronic source back in 2010. We deployed an EDC system as our eSource. We used it on hundreds of trials, until we became clients of Clinical Research IO. I was using eSource before it became commonplace. I never had a problem with it from sponsors or auditors, including the FDA.

Electronic source has allowed me to provide oversight and monitor the quality of work done at our other locations. It's cut down on errors, improved efficiency and allowed me to market our network to sponsors as a cutting-edge, high-data-integrity site. Just the other day, our QA Director was able to provide real-time oversight on a visit done by a relatively new coordinator.

> *"Electronic source has cut down on errors, improved efficiency and allowed me to market our network to sponsors as a cutting-edge, high-data-integrity site."*

SO WHAT MADE YOU DECIDE TO SELL?

In the fall of 2017, I received a cold call from a private equity firm that was trying to purchase clinical research sites. A few months later, another firm called me. That got me thinking that it might be a good time to sell. Both of the potential acquirers had heard of me from referrals.

After these inquiries piqued my interest, I spoke to a couple investment bankers. I talked to them and realized we were probably too small to warrant professional M&A representation. However, one of the bankers gave me the names of five institutional investors that were looking to buy firms with whom I'd make a good fit.

HOW DID YOU GO ABOUT SELLING THE NETWORK?

I reached out directly to the five referrals. I retained an attorney to help me navigate the negotiations and due diligence process. I signed an LOI with one of the firms, but as we went through the process, the potential buyer realized our accrued revenue was declining from the prior year, so re-adjusted the price downward. We ultimately couldn't agree on a figure, so I decided to walk away.

Coincidentally, at that time, a friend of mine who managed a large disability clinic network was in the process of working with private equity to help him significantly grow his business and one way to do that was to incorporate clinical trials. I still owned my disability clinics, so for me, this was an opportunity to exit both businesses, thus getting a better overall price. We ultimately closed in December 2018, and now I'm the Director of Research. My mandate is to grow the research business by partnering with the physicians in the existing network.

WHAT WAS THE SALE PROCESS LIKE? ANYTHING IN PARTICULAR SURPRISE YOU?

All the firms I spoke with use accrual-based accounting. Since I used cash-based accounting, we and they had to spend a lot of time converting my revenue figures from cash to accrual.

Overall, the due diligence these firms did was very rigorous. They reviewed my pipeline, my contracts, my payroll and expenses, and much more.

> *"My mandate is to grow the research business by partnering with the physicians in the existing network."*

They wanted projections going forward on all of my studies. I had to put together a spreadsheet for each study showing the projected visits for each of our existing patients, the number of future patients we could enroll and when those would happen. They also reviewed the studies we were awarded, and the studies we had submitted for but were not yet awarded. All of these projections led to a sophisticated revenue forecast model.

WE HEAR THAT PRICING FOR YOUR SIZE TIER MIGHT BE IN THE 5-7X EBITDA RANGE. WAS THAT WHAT YOU FOUND?

Yes, that's an accurate reflection of pricing.

WHAT ADVICE WOULD YOU GIVE A SITE OWNER LOOKING TO SELL?

First off, go to accrual-based accounting! It will give you the same vocabulary as the investors. Second, try to incorporate more rigorous forecasting as a process. If you have a good view of your revenue forecast, you can make an informed decision about when to sell your business and what type of price you could expect. You have to understand that your acquirer is going to do this exact exercise, and if they forecast a decline in revenue, your price will get adjusted downward.

Third, don't take any of the process personally. You may feel that in the due diligence process, everything you've been doing is being questioned. That's not the case. The acquirer is simply doing their best to understand your business and unearth all the risks. If, at the end of the due diligence process, the acquirer has a different view of the valuation, it's nothing to take personally. It's just the way the business works. Frankly, I would do the same in their shoes. Finally, because you know that the initial offer you receive is the highest valuation you could get, know what your walk-away price is. This will help you negotiate if the price is adjusted later.

WHAT ADVICE WOULD YOU GIVE A NETWORK OPERATOR LOOKING TO ACQUIRE – ESPECIALLY, AS YOU EXPERIENCED, WHEN THERE IS QUITE A BIT OF COMPETITION FOR GOOD SITES?

I think it's about listening to and understanding the desires of the site owner. If the site owner is looking for a clean retirement, then it's really just a matter of agreeing to the price. If they want to stay on, then it's about coming up with an appropriately defined role and compensation. The post-sale role of the owner will be critical to that person - they'll want to know their total comp, whether they get equity in the institution, and whether they see themselves working there, getting along with their colleagues, and buying into the vision. So being highly customized in your approach is key.

SPECIALIST BASED RESEARCH: A NEW VISION

From 2011-2017, Dr. Hans Hoeck served as CEO of CCBR, a 20+ site global research network that randomized 20,000 patients across multiple indications and was later acquired by a private equity firm. Under his leadership, CCBR built a significant site network in China covering participation of 250+ hospitals in 55+ major cities. Currently, Dr. Hoeck is CEO of Trialcare, an academic research institution with a unique vision for research. Prior to becoming CEO, Dr. Hoeck served as Managing Director of a major research site and as an academic physician. Dr. Hoeck received his MD from the University of Southern Denmark and his PhD from the University of Copenhagen.

TELL US ABOUT YOUR CAREER.

I was a specialist in Internal Medicine and Endocrinology and worked for 15 years in the public health care system mainly in university hospitals. Later, I had the opportunity to become the manager of a stand-alone clinical research site that was struggling. The site was part of a broader network of sites called CCBR. I was able to turn it around, and the founder entrusted me to serve as CEO. In 2012, the founder supported a growth strategy to globalize CCBR. During this period, CCBR added sites in Latin America and China. With the hard work of fantastic colleagues in different geographies, CCBR became a truly global site network. Since 2013, CCBR has been owned by different private equity firms.

AT CCBR, WHAT WERE YOUR MAJOR OPPORTUNITIES AND CHALLENGES?

At CCBR, we sold ourselves as a scientific, integrated PI network to global companies, including many U.S. based pharmaceutical sponsors. At first, we struggled because many of them characterized us as a "Site Management Organization," which at one point had a bad connotation since many of the SMO's in the early days were only doing business development, not operational management. Our scientific background and processes helped us to differentiate ourselves from that prior model. We emphasized the standardization of our operations across sites, which was essential to upscale our network in a relatively short time frame.

> *"We emphasized the standardization of our operations across sites, which was essential to upscale our network in a relatively short time frame."*

I used to think of CCBR's mission with respect to research as Starbucks's with respect to coffee: No matter which research site you enter, the standards and quality is the same.. For CCBR, this was quite an accomplishment because we were operating in a wide range of countries, with different languages, health care systems and cultures. In this context, we also benefited from being a member of the Society for Clinical Research Sites (SCRS), which provided all our clinic staff with access to online education and training independent of geography.

We weren't the only ones doing this in EU. Synexus was doing the same thing at the same time. But the site market has always been so fragmented that we never considered each other as competitors. It's such a big market out there with lots of opportunity for everyone.

AND NOW, "SITE MANAGEMENT ORGANIZATION" SEEMS TO BE AN OK THING TO LABEL ONESELF.

Yes, the term is not offensive any more. However, at the end of the day, the most important thing is to define how you want to present yourself to the marketplace – you need a clear statement of what your definition of value and delivery is all about.

YOU HAVE A SPECIFIC AND THOUGHT-PROVOKING VISION FOR THE FUTURE OF RESEARCH. TELL US ABOUT IT

First off, I don't believe we will eliminate the role of the local investigator, at least in the foreseeable future. You will always need a physician/specialist who is local to the patient to perform physical exams and provide safety oversight. The patients entrust their physician to make the right decisions and recommendations on their behalf and the PI will also, in the foreseeable future, be the patient's advocate to ensure their safety and well-being.
That said, I think we're at the point where we can almost eliminate the concept of a physical site facility. Of course, you need a place to work, see patients, store IP, etc., but now, if we can incorporate the right technology, we can do a lot of the data collection remotely. That means that while the PI will remain to perform needed in-clinic visits, we can foresee more at-home visits and more remote visits taking place within a trial.

What will make this happen is an end-to-end technology solution, from e-consent through data collection.

So, technology can replace the need to have a dedicated facility. More research can be done by specialty clinics as technology will reduce the physical workload on the clinic and clinic space dramatically. With more of a plug-and-play model, you could envision a larger, more dispersed network of specialists with interest in different kinds of research areas, who can participate as needed. These specialists don't need to have a large investment in local resources or infrastructure.

"I used to think of CCBR's mission with respect to research as Starbucks's with respect to coffee: No matter which research site you enter, the standards and quality is the same."

What that means for sponsors is that they can tap into the energy and interest of the many specialists out there who have an intellectual, but not necessarily financial, interest in performing research. And particularly for some indications, such as rare disease or some of the highly specialized indications, being able to tap into that very broad pool of physicians with access to the right patient population is critical. For high paying specialties, in particular, the financial incentive to do research is minimal. So engaging with these investigators on the level of scientific interest is critical.

A missing piece is the link between the Sponsor/CRO and the specialists/PI's. Current models are often not consistently effective and are one of the major causes for the study delays seen in most indications. Engaging with an independent academic research provider, who has a profound understanding of both sides' challenges and needs, is critical to achieving good, consistent performance.

We have witnessed this again recently with the formation of Trialcare, where we partner with highly recognized specialists and share harmonized workflows to ensure a level of quality in research commensurate with their daily clinical work. As an academic network operator, we share the core values of the specialists, which are to represent the interests of the patients and to put their safety and well-being as the highest priority. This also means that we only engage in sponsor funded research that can truly benefit our patients.

We work as the overall research umbrella, offloading a lot of the site administrative work with the assistance of technology. However, even with technology, a lot of specialized knowledge is required to run a trial efficiently. So there's a role for a sponsor-independent site operating partner with the roots in academia – perhaps call this the next version of the SMO model – who can partner with and quickly activate these specialists. These academic site operators will be well-positioned to encourage these specialists to professionalize their engagement in pharmaceutical and medical device sponsored research. These operators and the sponsors/CRO's can work more closely together, bridging critical gaps that are currently responsible for delays and insufficient performance of sites.

In this context, the right technology will move us toward an integrated end-to-end solution and increasingly enable us to minimize the workload of the sites. Having specialists to concentrate on the care of their patients will become more important. In parallel, as a member of SCRS, the site's staff will have access to a growing range of online education and training. Ultimately, sponsor funded research will then fit into the daily routine and become a natural and integrated part of a clinic, not a disruption.

THIS IS A BIG VISION FOR THE INDUSTRY. DO YOU THINK THIS WILL TAKE TIME?

Yes, definitely. The pace of change is slow, but everyone has the common goal to provide better treatment opportunities for the many patients in need. If you want to build a site network, or research operation, like we are doing with Trialcare, with this kind of framework in mind, you have to do so carefully and not grow too prematurely. That said, I think everyone should start thinking about a world of research where the elements I laid out are in place, and in that world, ask themselves how they are going to offer value.

IS THIS THE MODEL THAT WILL TRUMP THEM ALL?

Dustin Caldwell joined Optimed Research in 2013 when it was a single site in Central Ohio. He was initially appointed to improve efficiencies and modernize operations. In the past six years, Dustin has helped Optimed become a centrally managed, multi-site operation, covering nine states.

GIVE US THE STORY BEHIND OPTIMED RESEARCH

For 17 years, we were a stand-alone research site in Central Ohio. It was affiliated with a doctor's practice, and the site did a range of Internal Medicine studies. Starting in 2017, we changed the business model drastically. We created a nationwide, technology-based SMO. We took the legacy site in Ohio and folded it under this model. We've since expanded to 13 sites in nine states. We primarily seek to partner with physician practices. We look for engaged Investigators who may lack the experience or infrastructure to do research, and work with them to get their research function operational.

WHAT IS YOUR BUSINESS MODEL? WHAT MAKES IT DIFFERENT?

We have a very strong "center." The center does everything a traditional network operator does: source studies, negotiate the study contracts and manage the financials. However, we're also 100% eSource and eRegulatory enabled, so we go one step further. We design and push the eSource template to the sites, then we do all the QC and EDC entry centrally. We also manage the regulatory binders.

So, what we have is a very strong center and very lightweight, local hubs. We make it much easier for the local physician and coordinator to be successful. We need a lower threshold of revenue for each research site to be profitable. And we create economies of scale by centralizing the source design, QC, EDC and regulatory functions. These functions allow us to standardize critical parts of the workflow, thus ensuring high quality delivery to sponsors and CRO's.

> *"We need a lower threshold of revenue for each research site to be profitable."*

We also made one major change to the staffing model from the traditional SMO model: the coordinators are on the payroll of the Investigators. This recognizes the tight working relationship the two need to have, and gives the Investigators real "skin in the game" since they are paying for the coordinator salaries. Of course, we adjust our model so we take a lower percent of the revenue than we might otherwise take, but this trade-off allows us to scale quickly without significant capital.

"We also made one major change to the staffing model from the traditional SMO model: the coordinators are on the payroll of the Investigators."

HOW DO YOUR PIs PERCEIVE THIS MODEL?

They get a higher percent of the revenue, direct control over the coordinator resource, and a lot more centralized support than they otherwise might experience with a traditional operator. For instance, our eSource communicates directly with our Finance module, so as soon as the visit is done, the system knows exactly what is earned and outstanding.

For the Investigator, that means full transparency, full reimbursement on all procedures performed, and none of the usual burden of having to track activities in a spreadsheet or separate system.

WHERE DO PIs SOURCE THEIR COORDINATORS?

Many times, they appoint one of their trusted employees. At the beginning, they don't need a full-time employee, so this is a practical and cost-efficient way to staff. As they get bigger, they will need dedicated resources, and we will help them hire and train new employees as needed. That's a paid service that we provide.

With a fully tech-enabled platform, it's a lot easier to get a new hire up and running quickly since we take many of the operating workflows off the table. We can also QC their work quickly after the visit. If we have a relatively new resource, or someone who is struggling, we can provide very close to real-time feedback. That means we can recruit from a wider talent pool – we don't have to recruit exclusively from the small pool of experienced coordinators.

"Our eSource communicates directly with our Finance module...that means full transparency, full reimbursement on all procedures performed, and none of the usual burden of having to track activities."

DO YOU HAVE ANY PERFORMANCE METRICS THAT PROVE OUT THIS MODEL?

We do. We track a range of metrics, such as time to close a contract, first patient in, average EDC entry time, average query response time. On these and other metrics, we have shown that our brand new physicians – i.e. investigators doing their first study – are performing well above industry standard, and in fact are performing at the same level as you would expect of high-performing experienced investigators. And that's entirely because of our centralized business model. We have proven that our model is scalable – i.e., that by working with us, sponsors can experience uncompromised quality, regardless of the individual investigator's experience level. That means they can partner with us to select the right physician with the right patient population access.

THAT'S GOT TO BE VERY POWERFUL. HOW HAVE SPONSORS AND CRO'S REACTED TO THIS MODEL?

Positively, of course. More so the sponsors than the CROs. I think, in some ways, our business model encroaches on what CROs are supposed to deliver. But by gathering metrics and building proof cases, we know we're going to gain traction with pharmaceutical companies.

DID YOU HAVE ANY CHALLENGES TRANSITIONING TO THIS MODEL?

We did, at our legacy site. When we made the transition, we had to transform our core operations first. That meant introducing a culture of accountability and metrics. Many of our staff members resisted, so we ultimately had to effect a lot of turnover, and bring in personnel we could train from the outset. It wasn't just resistance to technology; it was resistance to transparency and accountability more broadly. But ultimately, you have to make choices, and we chose to pursue the right business model, rather than compromise on quality by catering to the most resistant.

ARE THERE ANY WEAKNESSES TO THIS MODEL?

We're still adjusting and learning as we go. But we are confident this is the right direction.

"We chose to pursue the right business model, rather than compromise on quality by catering to the most resistant."

CONTROLLING YOUR DATA: BUSINESS DEVELOPMENT IN A METRICS-BASED WORLD

Barry Lake is the CEO and co-founder of Devana Solutions, a business analytics, startup and metrics-capture solution for research sites and site networks. Prior to starting Devana, Barry ran a research site, where he personally experienced the frustrations of managing a complex pipeline of studies. Barry is a serial entrepreneur who has started and sold various companies in different industries but is presently focused on the clinical trials industry.

TELL US ABOUT HOW YOU STARTED DEVANA

The genesis was when I was running a site along with my main business partner and one of our key managers. We observed a lot of inefficiency in the study startup process. We didn't have a good way to track milestones from initially hearing about a lead all the way through award date, SIV date, first patient in and so on. At the same time, we began hearing from larger CROs that they were keeping metrics on our site including metrics on how fast we performed in start-up and, of course, screening and enrollment performance. We knew our site was a top performer in our core indications; but we learned that one of the largest CROs had our site on a blacklist, so we tracked them down. The person who maintained the database told us that we were a "zero enroller" on 6 studies. However, their conclusion was based on the fact we were awarded 6 studies; but, in reality, for various reasons, we never actually contracted for those studies. For example, in a couple cases we had competing studies so knew we might struggle enrolling on two very similar trials and, on a couple more, the budget being offered was not sufficient. For all six studies there were valid reasons we passed; but, that CRO's bad data was standing in the way of our site being considered for future trials.

Based on this painful experience, we quickly realized we needed to take control of our own site performance metrics. That's when we conceived of the idea behind the Devana Solutions technology. Our software enables sites to keep track of their study pipeline, track critical metrics such as turnaround time on feasibility, contracts, budgets and run reports across start-up milestones and enrollment performance. By the way, one thing we learned is that many of these CRO's, despite even their own size and sophistication, aren't using very robust systems themselves. Many times, it's their spreadsheet vs. the site's.

> *"Many times, it's the CROs spreadsheet vs. the site's."*

SO YOU KNOW A LOT ABOUT BUSINESS DEVELOPMENT. WHAT IS THE KEY TO BUSINESS DEVELOPMENT?

Obviously, you have to be a good site. Let's assume that for the sake of discussion.

For business development purposes, you need to develop strong relationships. Clinical Trials BD like all sales is very much a people game. A good business development professional is someone who can work independently, is self-motivated and can build and nurture relationships.

But, since it is heavily regulated, the clinical trials industry is very paperwork-intensive and study start-up can take a long time. From the time a site gets the first lead about a study to the time it receives an award letter and is greenlighted to begin enrolling, people at the site will, on average, interact with 7 to 8 different people from the sponsor or CRO. Part of this is because of specialized roles at each step of the process, and part of this is probably just natural position changes or turnover. So, a good BD person needs to navigate these relationships and transition effectively, and to do that he or she needs tools to efficiently manage workflows and continuously assess how the site is performing.

For that, you need some kind of a system to track and capture your site's own performance metrics. Why cede control of your destiny to someone else that says they're tracking your performance? You should have, at your fingertips, information on your pipeline, your past performance and the specific milestones and metrics of every study you're working on or have completed in the past and Devana technology does exactly that.

HOW MUCH DOES A BUSINESS DEVELOPMENT PROFESSIONAL COST? WHAT DO YOU DO IF YOU'RE A SMALL SITE?

My guess is they can range from $80,000 to $150,000 dollars a year depending on the market. Add conferences and travel, and you could be easily looking at a $200,000 annual investment. So, a dedicated BD role is something that usually requires a site generating $2 million of annual revenue or more.

For smaller sites, joining a network may make a lot of sense. That way, you're combining efforts and using that scale to invest in a business development function.

> *"Why cede control of your destiny to someone else who says they're tracking your performance?"*

WE HEAR A LOT ABOUT SITE METRICS. WHO IS COLLECTING THEM, AND WHAT KINDS?

A lot of people are collecting these metrics. The large CRO's and Sponsors are doing this. Software vendors are. Industry consortiums such as Transcelerate are likely taking steps in this direction.

At the site network I was a part of years ago, each month we'd meet with the top CRO's and review site study performance and the CRO's current pipelines. They were always tracking how our sites were performing in the start-up and enrollment process – how many patients each site screened, randomized, etc. Most of the CRO's were using their own systems to capture these metrics.

I want to stress again how important it is that sites track their own metrics. Because there are other study stakeholders trying to track progress, it's incumbent upon sites to be engaged in the dialogue and know their metrics cold.

WHAT DO YOU THINK OF THE RISE OF SITE NETWORKS? DO YOU EXPECT THIS TO CONTINUE?

Consolidation is here to stay, and here's why. The CRO consolidation is more or less done – the top 6 or 7 CRO's have emerged, and they control 70% of outsourced spending from sponsors. Many of the same financial investors that rolled up the CRO space are now rolling up the site space. I date the start of this trend to 2015, when PPD, through a related company, effectively acquired Radiant Research's sites and the next year, Synexus. But this trend still has a long way to go.

Most of these integrated site networks are looking for sites with $1 million in cash flow. Personally, I question how many sites of that scale are out there – maybe somewhere in the low to mid-hundred's in the U.S., based on analysis I've seen. Eventually, some of these networks trying to grow in scale may have to explore other avenues for growth such as greenfielding new sites or growing smaller existing sites.

WE HEAR THAT SPONSORS ARE STILL MAKING SITE SELECTION DECISIONS BASED ON INDIVIDUAL PI EXPERIENCE, AS OPPOSED TO THE OPERATIONAL CAPABILITIES OF THE SITE OR NETWORK. IS THAT THE CASE?

There is wisdom in stressing PI experience for rare disease trials because of access to patients. Over time, if integrated site networks achieve size and scale, I think the industry could shift from a PI-centric perspective to more of a site-centric view.

"Many of the same financial investors that rolled up the CRO space are now rolling up the site space."

WHERE DO YOU THINK WE'RE HEADING AS AN INDUSTRY?

I think data transparency is where things will go and, at Devana Solutions, we want to help lead the way. The best analogy to gauge where the clinical trials industry is headed would be to look at the history of the financial sector. Back in the 50's, there were no standards for determining who was creditworthy. Bankers would come to people's homes, perform interviews and make subjective decisions based on your neighborhood and even the quality of your existing furniture. You can imagine all kinds of problems arising from such a process. Then the financial industry came up with FICO scores standing for the Fair Isaac Credit Organization after the co-founders. Now, every lending decision is driven off that more objective measure, a common standard. If you think about it, we're doing investigational research on real patients, and lives are at stake. But there is no standard or uniform measure around site performance. That's got to change, and I believe that will change.

HOW RESEARCH CAN DRIVE VALUE-BASED HEALTH CARE: THE JAVARA STORY

Amanda Wright is Vice President of Partnership Development at Javara Inc., an integrated research organization (IRO) which partners with academic centers and health organizations to deliver research as an embedded option within a value-based care delivery system. Prior to joining Javara, Amanda was an executive at PMG Research, a major site network, where she began her career as a clinical research coordinator. Amanda serves on the board of Greater Gift, a non-profit that celebrates clinical research participation and connects participation to global health and well-being, and serves in a variety of industry advisory and leadership positions.

HOW DID JAVARA GET STARTED AND WHAT IS ITS MISSION?

Several of us had the opportunity to work together and understand the potential value of clinical research as part of value-based healthcare organizations, and we deeply believed there was a significant opportunity to help organizations realize this value. The initial founders came together to establish a service offering to major healthcare organizations and academic health systems to bring forth a degree of clinical research relevance that addresses the needs of patients, while also supporting a paradigm shift to achieve a more reliable drug development pathway.

Our mission is to partner with leading health organizations to integrate research into care delivery. We want to bring the right trials to the patients through their care teams, and thereby improve their own outcomes as well as align with the health organizations population health interests.

CAN YOU ELABORATE MORE ON HOW RESEARCH FURTHERS THE MISSION OF VALUE-BASED CARE?

Value-based care is all about measuring and delivering improved outcomes for patients and typically focuses on specific populations that generally are more complex to manage. It relies upon a more collaborative, team-based approach to delivering care.

> *"I think data transparency is where the industry will go."*

Research can be a natural fit to this team-based approach. If you think about it, clinical research is a high-touch, structured means of engaging with patients. In every trial, you're closely monitoring the patient's primary symptoms, their safety, and their medication adherence. This structure by itself promotes patient compliance with medication and other health regimens. It promotes open communication and understanding of the patient's needs. Even if the patient is on a placebo, participation by itself lifts patient outcomes. And because this is funded through pharmaceutical sponsors, it's delivered in a cost-neutral, even cost-offsetting, manner for the healthcare organization.

When we engage health organizations, we focus on their population needs, and bring a matched portfolio of research options to fit those objectives. For instance, we may focus on COPD and diabetes, because those are often large population health challenges where outcomes are highly responsive to lifestyle changes. By improving patient outcomes, we may reduce components such as costly emergency room visits.

THAT'S A COMPELLING VALUE PROPOSITION. BESIDES YOUR POSITIONING, DO YOU OPERATE YOUR RESEARCH DIFFERENTLY?

Yes, our research teams embed themselves into the healthcare organizations care teams. The most critical player for Javara is the "Clinical Trial Navigator." A Navigator does the work of the primary employed by on a trial, but that person is also a member of the care team that collectively cares for a given patient. For example, when our Navigator is screening a patient for potential trial eligibility, he or she may identify that the patient would benefit from participating in a care management program, or some other system initiative, and ensure appropriate communications occur within the care team. In this way, we serve as another touchpoint for the patient to reinforce the holistic, team-based approach to medicine that these systems are adopting.

HOW HAVE HEALTH SYSTEMS RESPONDED TO THIS NEW APPROACH?

It's been overwhelmingly positive. To date, most organizations have viewed research as a necessary loss leader to engage physicians who want to pursue it as a personal endeavor. We shift that framework. We position research as a population health strategy for the entire organization.

HOW HAS PHARMA RESPONDED? ARE THEY OPEN TO THIS APPROACH?

Yes. Many of them view our model and strategy as a very promising avenue to access patient populations, effectively engage patients and providers to contribute reliable data and shrink the life-cycle of drug discovery.

WHAT IS THE BIGGEST CHALLENGE WITH YOUR MODEL?

On the health organization side, it's mostly engaging with them when it fits their priorities. For instance, if the system is undertaking a major EMR transition, then they will likely put an initiative like this on hold.

"Our mission is to partner with leading health systems to integrate research into care delivery."

On the pharma side, it's mostly convincing some of the companies and/or decision makers to look past the relative lack of research experience of the investigators. As an industry, we have to change this mindset. We have to understand that most of what drives successful trial operations are the underlying processes, systems and teamwork of the staff, not merely the individual experience of the Principal Investigator. So when sponsors look at site-based research teams, they should consider the collective experience and capabilities of the team, not just the Investigator.

THAT'S HISTORICALLY BEEN A CHALLENGE WHEN WORKING WITH RESEARCH-NAIVE PHYSICIANS. ARE YOU FINDING THAT THIS MINDSET IS CHANGING?

Absolutely. There's a contingency within pharma who understand this and are eager to work with us to be part of a new found solution. For others, it will take some time and they will migrate to this model as additional data is available to demonstrate value through case studies.

SO YOUR INITIAL CASE STUDIES WILL BE CRITICAL.

Very much so. We are putting in place measurements to demonstrate the success of our initial trials. For the health organization, that means we work with them to measure outcomes on their terms E.g., patient outcomes, engagement scores, cost of care, etc.

Once we have the initial proof points, we're confident we can get the support of leadership at major health systems and pharmaceutical sponsors, and bring them together. That will make these concerns about research naivete recede quickly.

YOU'VE CHOSEN TO GO WITH YOUR OWN RESEARCH-SPECIFIC TECHNOLOGY PLATFORM, INCLUDING ELECTRONIC SOURCE, AS OPPOSED TO USING YOUR PARTNERS' EXISTING ELECTRONIC HEALTH RECORDS (EHR) SYSTEMS. CAN YOU ELABORATE ON THAT DECISION?

I certainly understand why a lot of people would view the EHR as a promising technology to capture source data. But most EHR systems aren't designed to capture research data at this time. In clinical trials, data has to be extremely precise and the way in which we collect this data is equally as precise. In research, it matters whether the blood pressure was taken after five minutes in the sitting position or ten minutes in the standing position, and you need structured templates to document these details. EHR systems, on the other hand, have a lot of unstructured data.

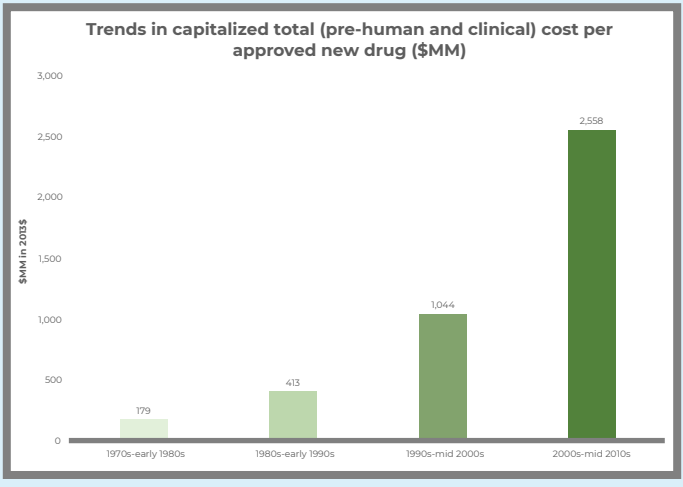
At some point, I foresee systems evolving so that eSource and EHR are integrated. But right now, the first step is to eliminate paper and adopt digitized workflow. It would be difficult to achieve our goals relying on a paper-based model.

"The most critical employee for Javara is the 'Clinical Trial Navigator.' A Navigator does the work of the primary coordinator on a trial, but that person is also a member of the care team that collectively cares for a given patient."

WHAT WOULD HAPPEN IF YOU SUCCEED IN YOUR MISSION?

There is a tremendous opportunity to drastically change the landscape of research when you consider how many volunteers the clinical trial industry needs each year. There's an emergence of organizations like us working to fulfill this need. It will take a lot of effort and different strategies to close the gap, and by doing so we can help bring more medicines to market faster for patients in need.

> *"We have to understand that most of what drives successful trial operations are the underlying processes, systems and teamwork of the staff, not merely the individual experience of the Principal Investigator."*



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