THE RISE OF THE CLINICAL TRIAL SITE MEGA NETWORK

Scaling and Innovating Part 3:

Site Network Consolidation by the Numbers

CRIO

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Introduction

By Raymond Nomizu

CRIO first published our Scaling and Innovating eBook in 2019, where CRIO predicted that research site networks would continue to grow and consolidate the industry. CRIO updated this first eBook with a second eBook in early 2023, which showed a marked increase in the number and breadth of institutional investors. CRIO's eBooks were primarily qualitative in nature, as CRIO didn't have reliable market data that quantified the degree of market consolidation that was taking place – until now.

At the October 2023 SCRS Global Site Solutions Summit, I met Colin Sholes of Cure Clinical. His company fuses data from the Sunshine Act with Clinicaltrials.gov, creating a database of every payment made to an investigator within a calendar year on a study by study basis.. Colin's team then normalizes the data, assigns each investigator to a site, and then assigns each site to a network.

Nelson Rutrick of Adams Clinical originated this concept. Nelson had been using a version of this approach for his own strategic planning purposes. Nelson seeded the idea with Colin, and Colin's team has turned the concept into a subscription license and consulting service.

Together with Cure Clinical, CRIO is proud to publish this eBook, our third in the Scaling and Innovating series: ***Site Network Consolidation By The Numbers.*** In this version, CRIO examines the consolidation of site networks, along with the size and growth of the for-profit sector of site payments in the United States.

It's important to note that, in compiling this data, CRIO relied solely on information that is publicly available. All revenue data is from the Cure Clinical database; all site network attributions are based on press releases and web searches. CRIO, Cure Clinical and Adams Clinical have no financial relationship with each other (other than that Adams Clinical is a client of CRIO). CRIO did make a significant contribution to the interpretation and classification of the entities.

The U.S. Site Market: An Overview

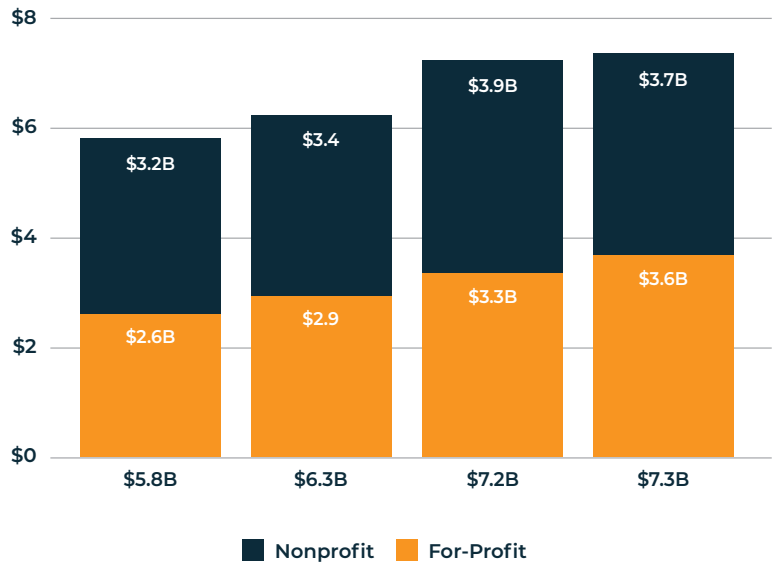
By Raymond Nomizu and Colin Sholes

Size and Growth

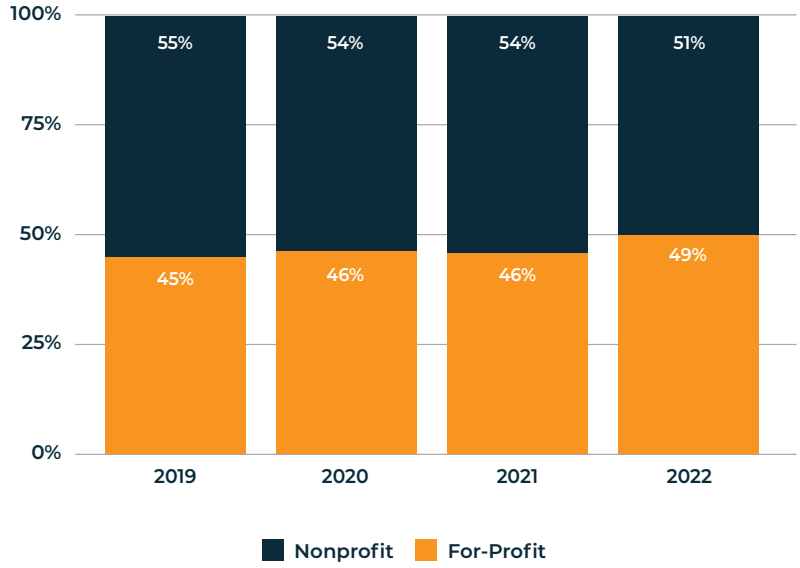
In 2022, total reported cash payments from industry to clinical research sites was $7.6 billion, of which approximately 50% went to non-profit organizations such as academic medical centers, hospitals and health systems; and 50% went to for-profit organizations such as sites and site networks, for-profit health systems, and integrated research organizations.

Over the 2019-2022 period, total site payments increased by 8.1% per year (compound annual growth rate). The for-profit sector grew more quickly, at 11.8% vs. 4.9% for the nonprofit sector. In 2019, nonprofits represented 55% of all research site spend; by 2022, that percentage declined to 51%.

U.S. RESEARCH SITE SPEND ($B)



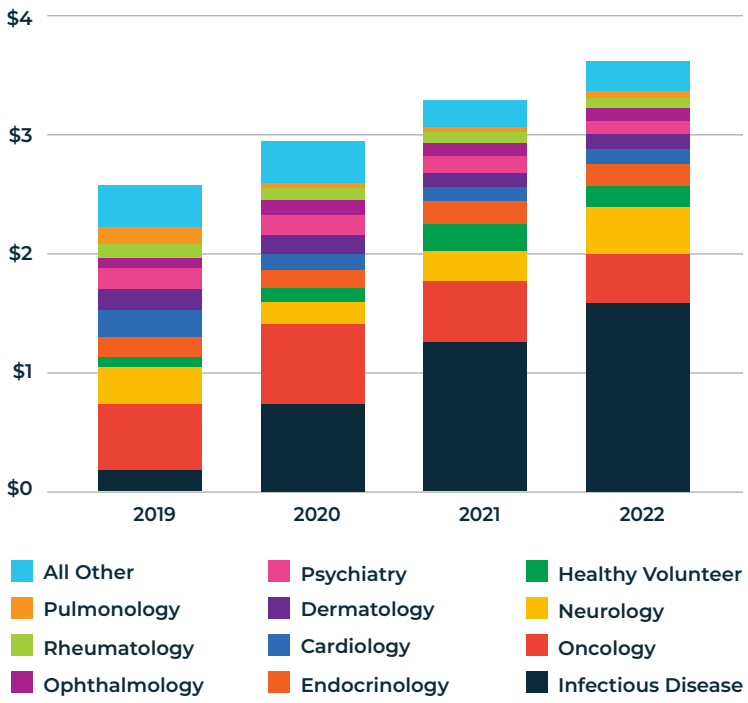
% OF SPEND BY PROFIT VS. NONPROFIT



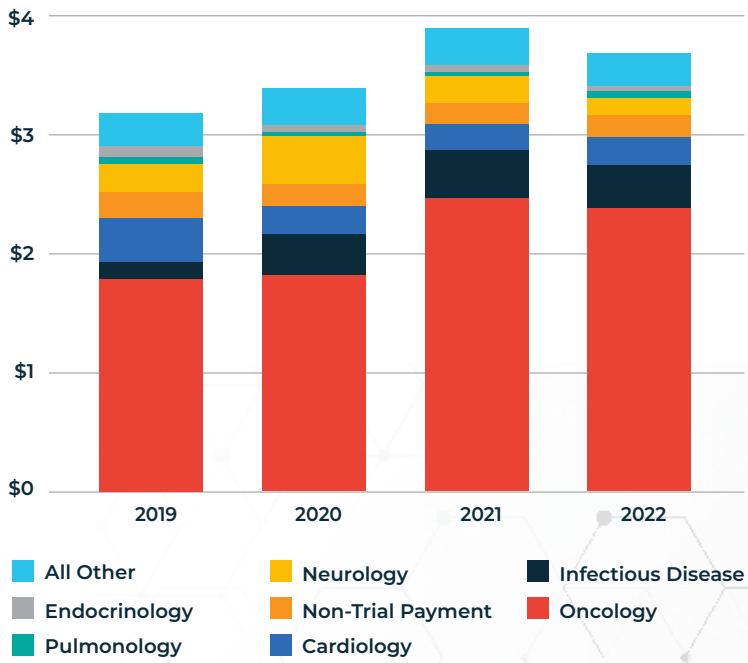
This differential growth rate was fueled by the rapid rise of mRNA-based vaccine trials, which are disproportionately done by for-profit sites. The chart below breaks out the revenue by therapeutic area[1] of for-profit sites:

By contrast, the nonprofit sector consists mostly of oncology, which grew much more slowly during this period.

FOR-PROFIT SITE REVENUE BY TA ($B)



NONPROFIT SITE REVENUE BY TA ($B)



[1] Studies that could not be categorized by therapeutic area were allocated in proportion to the ones that could. The total revenue for Uncategorized represented 8-24% of each year's total revenue.

Therapeutic Area Differentials

For-profit and nonprofit sites have different profiles; often, for-profit sites are higher enrollers and more efficient, especially with chronic conditions that have high prevalence in the population. By contrast, nonprofits, which include academic and cancer centers, often serve as centers of excellence, and therefore have access to more complex patient profiles.

As a result, most trials skew site selection toward one type of site, depending on the indication. Each sector has a different therapeutic mix, as seen by the following list of top 5 TA's:

FOR-PROFIT

1. Infectious disease	44%
2. Oncology	11%
3. Neurology	11%
4. Healthy volunteers	5%
5. Endocrinology	5%

NONPROFIT

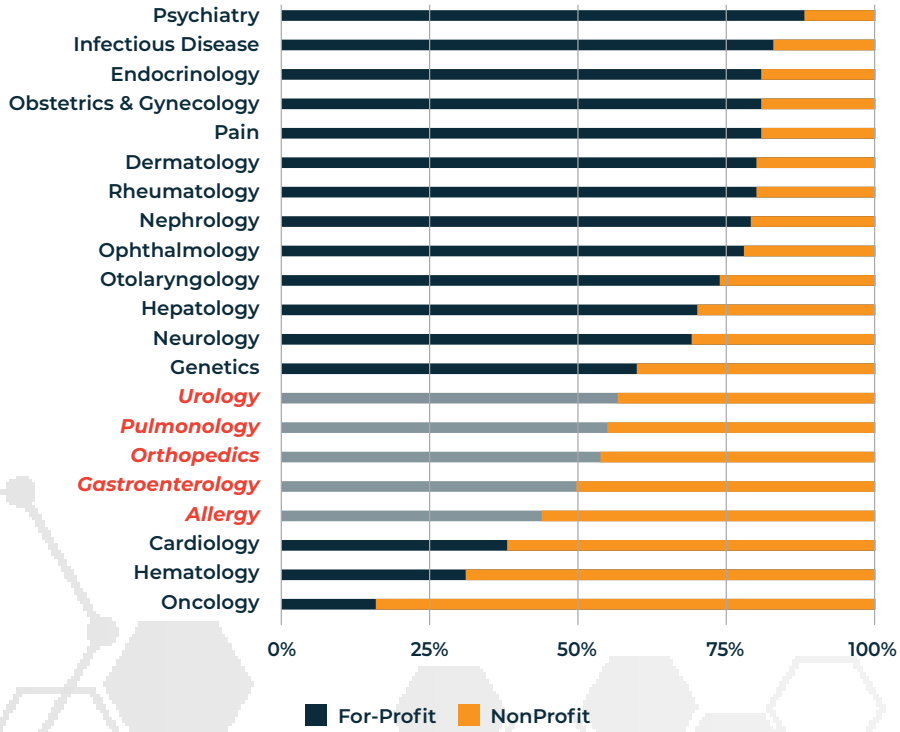
1. Oncology	65%
2. Infectious disease	10%
3. Cardiology	6%
4. Neurology	5%
5. Non-trial payment	4%[2]

[2] These usually represent blanket research grants not tied to a specific study.

Another way to look at the data is by showing the % revenue allocation between the two types of sites by therapeutic area. The following chart shows essentially a bi-modal distribution, with most therapeutic areas tending to be predominantly one segment or the other:

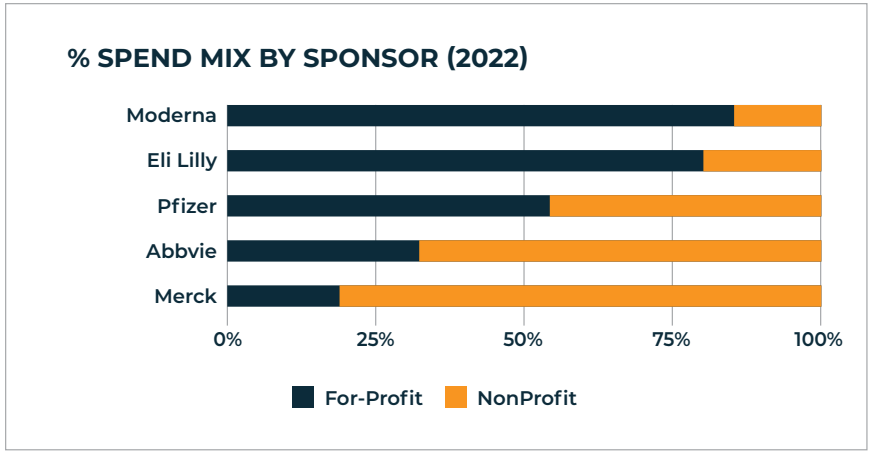
In the chart on the right, Urology, Pulmonology, Orthopedics, Gastroenterology and Allergy are the only therapeutic areas where there is a mix that is roughly balanced (between 40-60%).

% SITE SPEND BY TA (2022)



***Red & Italicized TAs reflect those that are between 40%-60% and therefore considered Roughly Equal*

We see the same bimodal distribution among sponsors as well. For instance, Moderna, which is primarily vaccine oriented, works with mostly for-profit sites, while Merck, which is oncology oriented, works with mostly Nonprofit sites.



Since therapeutic area and sponsor are aggregate categories, the bimodal distribution is likely even more pronounced at the individual study level. For instance, while Dermatology is 80% for-profit and 20% nonprofit in distribution, it likely encompasses a large number of studies in indications like atopic dermatitis that run 95% for-profit site selection, with a smaller number of studies with more complex indications that run 50% or more nonprofit site selection. The latter group of studies might involve conditions that are so severe or rare that they necessitate use of centers of excellence.

Site Consolidation: By the Numbers

By Raymond Nomizu and Colin Sholes

Rise of Financial Investors

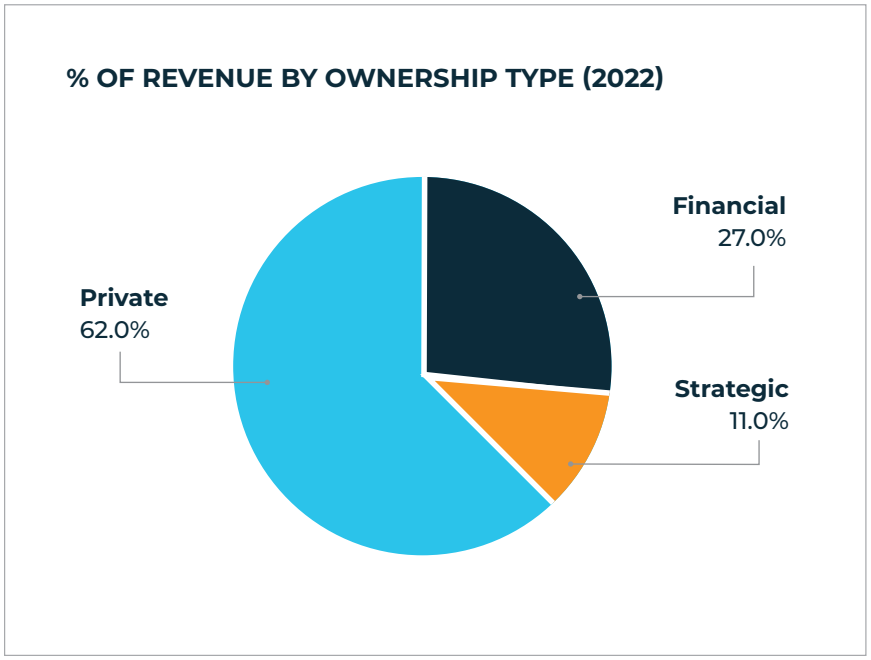
We classified all parent entities within the for-profit sector by the type of ownership. We believe this is a salient characteristic because each ownership type shows different behavior.

Financial: This is defined as any institutional investor, typically private equity but sometimes venture capital. Financial investors need to grow, often seeking to triple or quadruple the value of their holdings over a 5-7 year period, and the fastest way to do this in the site industry is through acquisition.

Strategic: We categorize this as a corporate parent with a different primary business than research sites; typically these are CRO's, health care providers, or pharmacy chains. Strategic owners view research as an extension of their core business, and while they likely have set growth targets, they often hit a maturation point in their growth.

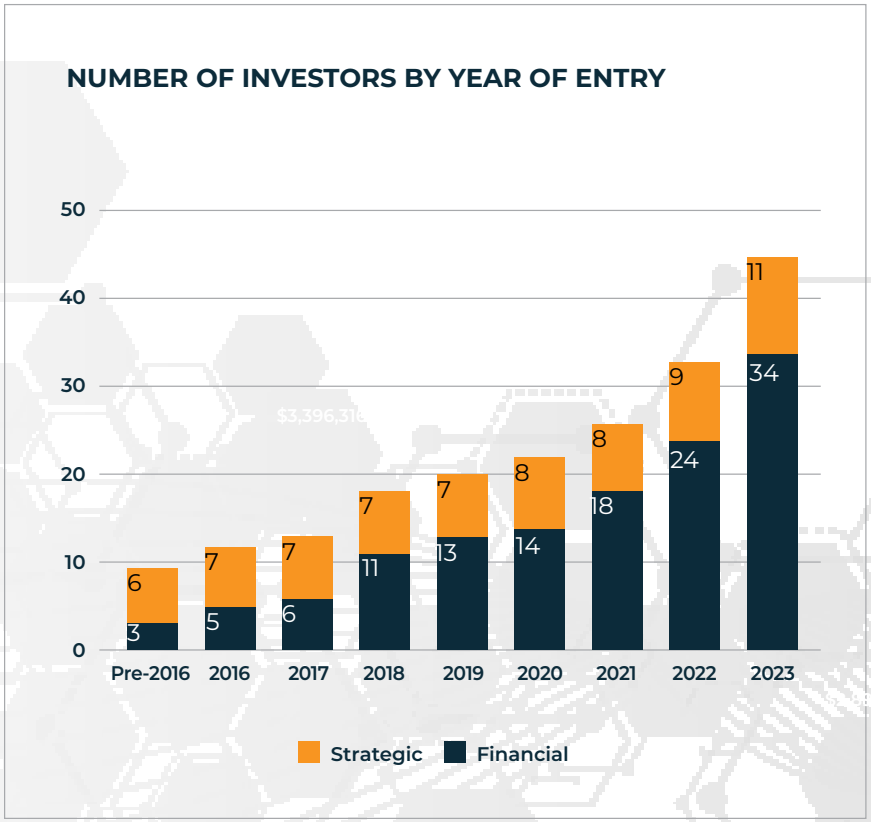
Private: This encapsulates everyone else - essentially, private individual ownership. Private investors can have any number of objectives, from growth to profit maintenance. However, given that we are talking about individuals who may not be fully liquid, private owners tend to pursue more capital-efficient and organic growth-oriented strategies.

When looking at U.S. site revenue by ownership type, we classified Financial and Strategic ownership as 38% of total 2022 revenue, with Financial at 27% and Strategic at 11%.



Financial Investors Are Driving Consolidation

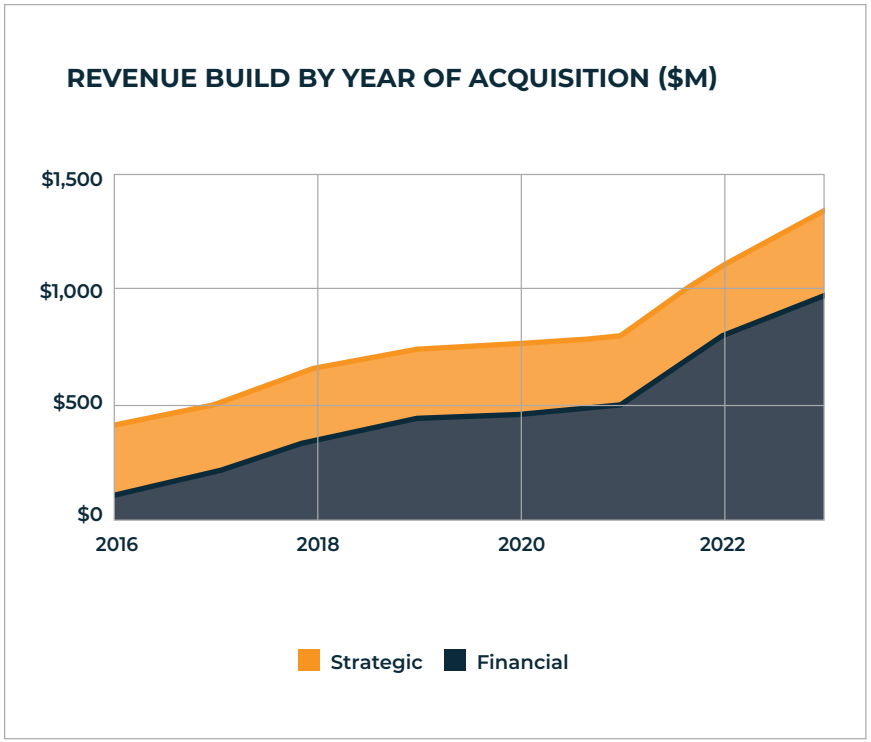
An increasing number of financial investors have entered the clinical research site consolidation business, as the following chart shows:



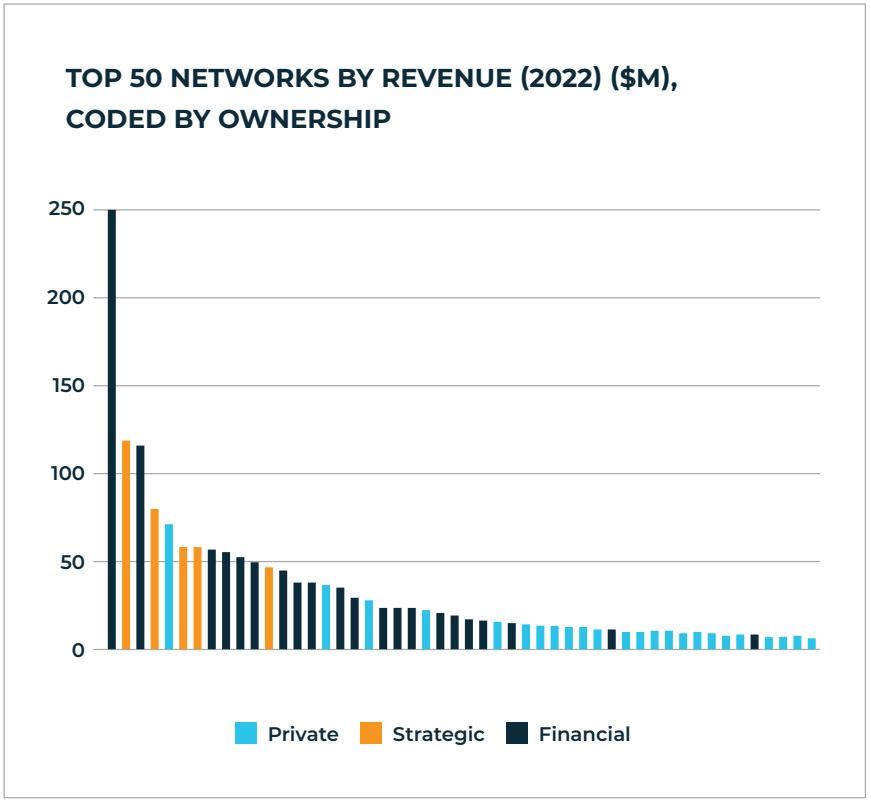
As of the date of this report (Nov. 2023), there are 34 unique financial investors who serve as majority or lead investors in a site network, and, anecdotally, over 100 additional investors exploring the space . This represents a dramatic increase from 2015, when there were only 3 active investors.

Financial investors have been far more acquisitive than strategic investors. One way to measure the rate of acquisition growth is by modeling the revenue ramp over time based on the year in which the network acquired a given site. The following shows the implied revenue growth from acquisition for financial vs. strategic investors as a whole:

As the chart shows, financial investors currently own sites that generated 2022 revenue of $971MM ; without any acquisitions, this same investor class would have generated 2022 revenue of $81MM based on their 2016 footprint, implying 36% compound annual growth via acquisition. This CAGR is in line with typical private equity expectations, and implies a near-doubling every two years.



Furthermore, the largest players in the industry are mostly financial, as the following chart of the Top 50 Networks by revenue shows:



Market Segmentation and the Private Segment

How fragmented is the private segment? On the surface, it appears highly fragmented, but when compared to the number of financial investors, there are a rapidly dwindling number of viable acquisition candidates.

We counted approximately 70 site networks that are privately owned with $5 million or more in revenue - these represent attractive *platform* candidates for financial investors.

We counted approximately 200 site networks that are privately owned that generated at least $2 - $5 million in revenue - these represent attractive *add-on* candidates for acquisition.

And we found an additional 300 site networks that are privately owned that generated at least $1 - $2 million in revenue - these represent *up-and-coming* candidates for acquisition.

Altogether, there are about 600 privately owned sites with $1 million or more in annual revenue; this midmarket constitutes 46% of total site revenue. Within this group are some of the future network leaders.

When we went below the $1 million revenue mark, there were thousands of research sites - almost 9,000 in total, but a significant number had de minimis payments and therefore are not likely *true* businesses. The de minimis payment (e.g., <$20K) likely indicates a stub-year payment for an investigator who is exiting the business or, potentially, a coding error. Most likely, we estimate there are about 4,000 “true” research sites below the $1 million mark.

Putting it altogether, we end up with the following segmentation:

Segment	#	Rev ($M)	Share	Avg ($M)
Enterprise (Financial/Strategic)	45	$1,350	38%	$30
Mid Market ($1M rev & up)	600	$1,650	46%	$3
Small (Sub $1M rev)	4000	$600	17%	$0.1-$0.2
Total	~4,645	$3,600	100%	$0.7

What does this mean?

We believe about 20 of the current financial investors are acquisitive, and there are several more who will enter the market soon. Given the imperative of growth, if we assume that 20-25 active investors need to make 3-4 site acquisitions per year, we could estimate there is demand for 80-100 site acquisitions per year. This means we have only 3 to 6 years of "acquisition inventory" left (270 companies with $2M+ revenue, or double that with $1M+ revenue).

Of course, many owners will choose to remain private, and there will always remain a segment of the market for high-performing independent sites with unique patient population access. So most likely, sometime in the next 3-5 years, financial investors could reach a saturation point where financial owners have doubled their ownership stake, and begin merging with each other.

We'll explore some of the implications in our next article.

List of Financial Investors

Site Network	Current Owner / Investor
Alcanza Clinical Research	Martis Capital
Alliance Clinical Network	Amulet Capital Partners
AltaScience	Novo Holdings
American Clinical Research Services	Latticework
AMR LLC (Alliance for Multispecialty Research)	Curewell Capital
Atlas Clinical Research	BPOC
Care Access Research	Venture Capital
Celerion	HIG Capital
CenExel	Webster Capital
Centricity	Trinity Hunt Partners
Circuit Clinical	Venture Capital
Conquest Research	Reynolda Equity Partners
Elite Clinical Network	SurgePE
ERG (evolution research group)	Linden Capital Partners
Eximia	VSS Capital Partners
Flourish Research	NMS Capital
Futuremeds	Dealspan

Site Network	Current Owner / Investor
Headlands	KKR
Helios	Grant Avenue Capital
IMA Group	Centre Partners
Javara	General Atlantic
Johnson County Clin-Trials	FFL Partners
Monroe Biomedical Research	New Harbor
Nucleus Network	Blackstone
Objective Health	TKS
Pacific Clinical Research Trials	Pencarrow
Panthera	Gresham House Ventures
Pinnacle Clinical Research	LongueVue Capital
Profound Research	Rubicon Founders
Sitebridge	Health2047 (AMA)
Tekton Research	Havencrest
Topography Health	a16z
Velocity Clinical Research	GHO Capital
Wake Research Associates	M3 Inc.

List of Strategics

Site Network	Type
Fortrea	CRO
ICON (Accellacare)	CRO
IQVIA (Avacare)	CRO
Parexel	CRO
PPD AES (Synexus, BioClinica)	CRO
CVS Health	Pharmacy
Kroger	Pharmacy
Walgreens	Pharmacy
Davita Clinical Research	Provider
Frenova	Provider
McKesson	Provider

Where do we go from here?

By Raymond Nomizu

The analysis in this ebook shows that financial and strategic investors already represent nearly 40% of the market, with only a few years' "supply" of platform and bolt-on acquisition candidates remaining.

In the following summary, I'll make some predictions. These are my predictions only, and entirely subjective.

1 In the next 3-5 years, financial investors will hit market saturation, and in the following 5 years after, start merging with each other to create mega networks

Already, financial investors constitute 27% ownership of the market, and if they were to double their percentage share, then, with Strategics, they would own two thirds of the market. At this point, the most logical growth path would be for the networks to start merging with each other.

This follows from the core business logic of site network consolidation. Network mergers create scalability on centralized functions; diversify risk through broader geographic and therapeutic area reach; and enable the networks to field entire studies (at least the U.S. portion), which give them more leverage. For research sites, scale is best achieved at the global and national levels, not state or regional.

For these reasons, we could end up with 5-10 mega networks accessing 70-80% of active investigators in the United States, and some portion of the rest of the world - and this will have significant impact on the industry.

2 Mega networks will diversify service offerings

The mega networks will end up diversifying their service offerings beyond brick-and-mortar sites. I see three sources of expansion:

1. **HEALTH SYSTEM BUSINESS PROCESS OUTSOURCING (BPO).** Already, integrated research organizations like Javara, Elligo, Circuit Clinical and Objective Health have proven the viability of partnering with healthcare institutions to launch and run their clinical research operations. Besides these bottom-up partnership approaches, there could be another avenue for networks to tap into health systems (i.e., nonprofits) through BPO. A network could strike a deal to take over existing research operations of a health system, transferring their employees over. This would allow the network to extend their study pipeline and financial management, while enabling the free flow of research talent across institutions.

2. **DECENTRALIZED TRIALS.** Site networks will partner with and/or acquire home health care service providers for in-home trial opportunities. Some site networks will also establish virtual sites, and may even repurpose their existing PI's to become virtual PI's. Coupled with health system BPO and DCT delivery elements, site networks will now be able to effectively sole source entire studies.

3. **CENTRAL RECRUITING.** Site networks with nationwide footprints will develop centralized recruitment strategies to support their studies. Some will end up purchasing recruitment firms, or developing their own capabilities, and some will make these recruiting services stand-alone offerings.

3 Mega networks will become CROs, or merge with CROs

All of the levers above are near-term expansion opportunities. But ultimately, the site networks will realize that as they become large enough to source all the patients for a trial, they can go up the value chain and start selling studies from end to end. Already, networks can perform many of the traditional roles that CRO's have done in terms of site selection and budget standardization. With additional central capabilities, and some organizational guardrails, networks can start offering study start-up, monitoring and data management services. Networks will realize that there's another pool of money they can tap into, and they can access this pool more efficiently than third party CROs. Some will, therefore, add CRO capabilities, combine with a CRO, or a CRO may anticipate the shift in market dynamics and make an acquisition bid for a mega network. This new, site-powered entity might be the "next generation" Contract Research Organization.

4 These next generation network-based CROs will implement tech-enabled clinical trials - and transform the industry

Site networks at this scale have to be tech-enabled to succeed. They will implement and manage their own technologies to manage every aspect of clinical trial operations. The tech-centered approach will allow them to manage workflows centrally, allowing them to scale efficiently across multiple locations. With stronger central operations, their local site personnel (mainly investigators and coordinators) will only have to focus on patient-centered activities such as protocol execution, data collection, eligibility screening or patient retention. For more information on the technologies networks should consider, read our blog post here.

The most significant change is that networks will replace antiquated paper-based processes at the site level with eSource, electronic Investigative Site Files (eISF) and eConsent systems, and then begin integrating (or driving integration of) these systems with both health system EMR systems and sponsor and CRO-driven solutions. This site-centered technology platform will eliminate much of the manual data capture, duplicative data entry and login management that sites have to contend with.

Not only will these efficiencies benefit site operations and patient care, but they will create unprecedented efficiencies for sponsors, who currently spend a significant portion of their clinical trial budget on monitoring, data management and quality assurance-related activities to ensure that site collected data is accurate and up to date. If sponsors can get reliably and consistently higher quality data at lower cost, and on a real-time basis, they can significantly shorten time to market for new drugs.

As a result, large site networks that successfully implement these platform technologies will be in a position to re-sell more efficient, tech-enabled and data-rich solutions to sponsors - thus making them formidable competitors to traditional CRO's that have come to rely on manual processes to correct for the inefficiencies of a historically fragmented, paper-driven research site market. This competition will transform the industry for the better - and finally deliver the savings in new drug development costs that have eluded drug development firms and policymakers for decades.

Our Methodology

By Colin Sholes

Our database utilizes Open Payments data reported under the Sunshine Act. The Sunshine Act requires all pharmaceutical and device sponsors with an approved drug or device on the U.S. market to report investigator payments for the previous calendar year. On June 30, 2023, CMS released this information for the calendar year 2022.

The Sunshine Act applies only to payments made to U.S. investigators. Our data does not include investigator revenue for sites located in Canada, Europe, Australia or elsewhere. We note that many investor-led networks are active in these markets.

There are some limitations on what is reported:

1. Despite no carve outs in the law, phase 1 reporting is sporadic; some sponsors report, some do not. There are no significant penalties for noncompliance.
2. Sponsors without a drug or device on the market do not have to report; small biotechs and early stage startups will not appear in the data. The most notable example is that Moderna did not report in 2020, as its vaccine was not approved until 2021[1]. There is not a retroactive reporting requirement, so data only carries forward from a sponsor's first reporting year.
3. Only payments to licensed doctors and nurses are recorded; principal investigators who are PhDs or PsyDs will not appear. This results in a small undercount, especially for CNS and Psych studies.
4. Among late stage trials, there is still not total compliance; we identified one sponsor who does not appear to have reported payment data for any of their trials.

Still, Open Payments data is by far the most comprehensive and accurate data on investigator payments, with the added upside of being publicly verifiable. Every major global pharmaceutical company participates, and it provides a robust snapshot of the US research landscape.

For 2022, we matched 90% of study payments to clinicaltrials.gov data, and for these matched studies, we incorporate available metadata such as phase, protocol number, therapeutic area, disease, and drug.

[1] In our aggregate market size analysis, we increased 2020 site revenue by assuming that the Moderna trial had similar payments to its Pfizer equivalent, and allocated that revenue 95% to for-profit and 5% to nonprofit based on their reported site selection mix.

Due to the diversity of companies reporting payments, investigator and site data is not normalized in the Open Payments file. We spent considerable time normalizing investigator names and addresses, using the investigator's NCI number as a unique identifier. We also cleaned and organized research site names, assigning sites to parent entities (i.e., networks) by using publicly available data on network acquisitions. We then coded each site and parent entity as for- or non-profit.

While the data is extremely reliable in the aggregate, it may not be reliable for an individual site, as exclusion of a single study could result in material under-reporting. Our database's reported revenue should be viewed as the minimum for any one site or investigator.

Finally, we should note that Open Payments only captures payments made, so given current industry practices of holdbacks, and 60-120 day payment cycles, there can be a significant lag between the time a site recognizes revenue and the time it receives payment. For instance, it's possible that 10% of the payments made in 2022 relate to holdbacks associated with study procedures completed over the past 1 to 5 years, and the balance relate to study procedures completed from Q4 2021 through Q3 2022.

We also note that the actual revenue mix reflects a study pipeline snapshot. We treat our data as directional, and note that it cannot be used to accurately predict future revenues.

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