The CenterWatch Monthly

In This Issue

September 2024 A CenterWatch Publication Volume 31, Issue 09

Editor's Note: After 30 years of serving the operational and professional development needs of clinical researchers, *The CenterWatch Monthly* presents its final issue. On behalf of myself and the editorial and production teams, I would like to thank you for your support and readership. We are grateful for the opportunity to have served you. – Leslie Ramsey, Editorial Director

Sponsors Face Fewer Financial Hits for Drug Delays Today, New Data Show

By James Miessler

The average daily cost for trials and drug development delays has dropped considerably for sponsors over the years, new data from the Tufts Center for the Study of Drug Development (CSDD) show, owing to a number of factors.

The center's latest Impact Report, which updates a number of outdated financial measures, is likely to be practicable for stakeholders from a strategic business perspective, says Ken Getz, executive director of Tufts CSDD.

"Financial measures of the value of time are very important for drug development professionals. These measures are used to inform return on investment (ROI) in new practices and solutions, and they inform budget and resource planning decisions," Getz told *The CenterWatch Monthly*. "The two most frequently used measures, the average value of a day of lost or delayed prescription drug sales and the average direct daily cost to conduct a clinical trial, are antiquated estimates that are more than 30 years old."

"We anticipate that the new and unexpected financial value measures from this study will significantly impact ROI calculations and budget and resource planning decisions," he continued. "This may result in companies limiting or curtailing investments and deployment of staff and resources given budgetary pressures and the current global economic climate."

The report reveals that running later-stage trials in today's climate costs about $40,500 daily when adjusting for inflation.

see **Trial Costs** on page 5

FDA Must Overcome Barriers to Sharing Confidential Information, Experts Say

By James Miessler

The FDA has long erred on the side of extreme caution when it comes to sharing confidential commercial information and trade secrets out of fear it might violate federal law by disclosing them.

But these fears are in some ways unfounded, and for the benefit of medical advancement and public health, it is time for the agency to reassess its approach to releasing such information, two Harvard experts say.

The Freedom of Information Act (FOIA) and the Trade Secrets Act, the two main laws that dictate how the FDA can communicate with the public, have led to stringent agency regulations constraining its ability to disclose valuable information, say C. Joseph Ross Daval, attorney for the Harvard Brigham and Women's Hospital's Program on Regulation, Therapeutics and Law (PORTAL), and Aaron Kesselheim, the program's founder.

But the agency can and should take action to arm itself with greater but cautious flexibility in this regard, they write in a *JAMA* Viewpoint article.

"The relevant principles covering disclosure of confidential commercial information encompassed in these statutes appear to give FDA broad authority to share information it obtains from private companies — if it so chooses," they write. "FDA can take steps to allow itself more flexibility to share information in the interest of public health."

see **Confidential Information** on page 6

The Biotech CFO's Secret Lever: Optimizing Clinical Trial Agreements

In the rapidly evolving and competitive biotech industry, where innovation and financial performance are inextricably linked, savvy CFOs must adopt a long-term perspective to navigate the complex, often decade-long journey of drug commercialization, says ***Karl Dorwart****, vice president, head of healthcare, life sciences and consumer staples at Factor, an integrated law provider.*

From discovery to market launch, development timelines require strategic financial planning and adaptability at every stage. Within this frequently prolonged development cycle, an often-overlooked tool emerges as a critical lever for success: the optimization of clinical trial contracting.

Optimizing trial contracting can serve as a catalyst for accelerating innovation, reducing costs and boosting revenue. As biotech companies scale, the volume and complexity of legal work increases, requiring strategic planning to enable and execute the multijurisdictional trial contracting process efficiently.

For early-stage biotechs in particular, effective trial contracting is mission-critical to accelerating the initiation of trials and expediting enrollment. This efficiency not only benefits patients by providing earlier access to potentially life-changing treatments but also sets the foundation for generating the efficacy and safety data needed to obtain approval and market access.

The financial implications of speeding up the contracting process are also significant. Accelerating revenue realization by reducing time to market can mitigate losses of up to $8 million a day associated with trial delays and budget overruns, according to research published in the *Journal of Clinical and Translational Science* in 2023. Moreover, efficient contracting practices established early can help manage and stretch limited resources over the long development cycle, facilitating more predictable cash flow projections crucial for long-term financial planning.

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CFO Role Expands to Legal Operations

As biotechs face increasing pressure to innovate while managing costs, CFOs are stepping beyond their traditional financial roles to become strategic partners in operational efficiency. By maximizing the high-yield revenue opportunity in clinical trial contracting and legal operations, CFOs can drive cost savings through process optimization and vendor management.

Planning legal operations early in a biotech's journey is crucial. Implementing legal and contracting templates, playbooks and technologies with a focus on ROI can lay the groundwork for efficient operations and scalability and guide hiring and resourcing decisions as pipeline programs move through later clinical stages.

One recent example of a clinical stage biopharmaceutical company illustrates the challenges and opportunities in optimizing trial contracting. This company, which develops a novel class of medicines for diseases that are underserved by existing therapeutics, needed to quickly scale trials across several hundred sites and numerous geographies.

The company's existing contracting model was split between CROs perceived as lacking the necessary contract negotiation expertise and a large law firm as the escalation and enablement partner. However, the law firm was seen by the company as an expensive and overly risk-averse solution. The company had additional pipeline drug candidates that would soon be moving into clinical development in similar jurisdictions and comparable sites, and further dependence on a law firm would become prohibitively expensive.

In its search for an optimized trial contract process, the company recognized the value of the cumulative efficiency gains of investing in a scalable, repeatable contracting model to support the company's growth trajectory, versus further committing operating expense and brute force to simply get the work done.

Instead, by investing in a flexible and scalable model, this company was able to work with a third-party partner to integrate the talent, expertise and technology needed to develop contract templates and interactive playbooks to sup-

see **Viewpoint** on page 6

‘Boutique’ SMO Owner Talks Managing Multiple Sites from Afar, Juggling Tech and More

While today’s technology has brought many incredible efficiencies to the clinical research landscape, tech management strategy is more important than ever before, especially at the site level. ***Alisha Garibaldi****, CEO of Skylight Health Research, a company that runs three US sites, linked up with The CenterWatch Monthly to discuss navigating technology, her unique way of doing business, how she’s able to run her network from Canada and more.*

CWM: *Skylight considers itself a “boutique site management organization (SMO).” Can you describe this type of organization, the services Skylight offers and its clientele?*

AG: I refer to Skylight as a boutique SMO because we have three different locations but are still a small company overall, and unlike a lot of SMOs, we own our sites. Similar to an SMO, we can launch a trial at multiple locations under one contract and budget, but with a single regulatory contact on our end to streamline and simplify efforts for sponsors and CROs. Being a small company allows me to remain involved and hands-on in the day-to-day efforts of conducting clinical research, and I like to remain easily accessible when it comes to communicating with sponsors and CROs. Right now, we have a great balance between maintaining the infrastructure of a large corporation or SMO and still operating with the dedication and responsiveness of a small startup.

Our operating model developed naturally from our roots starting as a department within a primary care organization. At the time, the organization had about 30 primary care clinics throughout the US, and I was brought on to establish a research department. My role was to take this network of primary care sites and centralize infrastructure to conduct research, making it simple for providers, accessible for patients and streamlined for staff.

> “The industry has seen massive advances that are fantastic and beneficial, yet the volume of new technology can lead to complications that are challenging for sites. It's hard to maintain the different systems, know every single login and remember what each tool is used for.”
>
> — Alisha Garibaldi, CEO, Skylight Health

In 2021, we launched three sites in centralized areas to create a network and allow more patients to participate in our studies. Two years later, we went independent from the primary care organization. It was a very natural progression to start within this larger organization, separate out and maintain that model of making research accessible through our centralized infrastructure. We currently operate with two true standalone sites in Burlington, Mass., and Colorado Springs, Colo., and one site in Harrisburg, Pa., that is integrated with a primary and urgent care clinic.

CWM: *I understand that you personally are based in Canada. Please tell me more about managing three US sites from another country.*

AG: When I joined the primary care organization to launch its research arm, I was part of the small corporate team within Canada and once Skylight Health Research became independent, we maintained the business in the US. Achieving this boils down to two key factors: people and technology. I have an absolutely incredible team on the ground in the US who I trust fully to execute our trials, and thanks to advanced technology, I can operate remotely with a lot of efficiency.

Technology also enabled me to mitigate the regulatory hurdles of working remotely. Implementing an electronic investigator site file (eISF) system made a significant difference here. I cannot stress enough how much it has simplified our operations, allowing me to manage all regulatory files remotely. I couldn't do that if we were on paper binders; I would be spending so much more time traveling to my sites to ensure our ISFs are up to date and audit ready. The alternative would be to have a regulatory specialist on-site at each location to allow my investigators and coordinators to focus on the patients and not the paperwork.

CWM: *Technological developments have advanced rapidly this year. How has Skylight been keeping pace with these changes?*

AG: I've been in research for almost 15 years. I come from a time when you had to fill out paper case report forms and fax them in so someone could validate data on this very archaic program. Today, if I have

see **Tech Management** on page 7

Despite Small Size, Rare Disease Trials Can Have a Big Impact on Medical Advancements

By Mike Ingram

Rare disease advocacy groups often use the phrase "rare is not rare" to drive home the point that, although individual diseases and conditions might affect only a small number of people, together they constitute a large patient population.

To put it another way: "Rare diseases are individually rare but collectively common," researchers at the Mayo Clinic wrote in a paper they published last year.

The NIH defines a rare disease as a condition that affects fewer than 200,000 people in the US. That's the same benchmark Congress used in the 1983 Orphan Drug Act, which set up special rules for drugs and devices aimed at these diseases to encourage and incentivize clinical research in the rare disease space.

According to the Mayo Clinic, between 25 million and 30 million Americans live with a rare disease.

The importance of clinical research for rare disease treatments isn't limited to treating the rare diseases themselves. "Rare diseases are model diseases for scientific breakthroughs," the Mayo authors wrote. "Some of the most important drug discoveries benefiting large segments of the population were made due to improved understanding of a rare disease."

Statins, for example, were first developed following discoveries related to the molecular causes of homozygous familial hypercholesterolemia, which affects only one in a million people in the US, the authors note. But some 28 percent of American men and women over the age of 40 today are prescribed statins to help control their cholesterol levels.

Despite the importance of rare disease research, a number of factors make it difficult to carry out, experts say. For one, the small number of affected patients can be a challenge for recruitment. And since potential subjects likely live in different parts of the country — and the world — geographic and financial factors may limit their participation.

"Even patients who are motivated to help find a cure for their disease may choose not to participate because the logistics of participation — e.g., travel to a far-away clinic, frequent medical tests, incompatibility with job requirements or with other medications — make it too burdensome," Sally Lanar of ICON and colleagues write in the Orphanet Journal of Rare Diseases.

Only about 3 percent of diagnosed rare diseases have suitable drug treatments, researchers from the Hong Kong Genome Institute and the University of Hong Kong wrote in Frontiers in Public Health in October 2022. This is due, in part, to a lack of market incentives for developing these therapies, they wrote. And when drugs for rare diseases are developed, they can cost as much as 13.8 percent more than conventional drugs.

"This can be financially overwhelming for many, especially when rare disease drugs usually require out-of-pocket cost-sharing by the patient," the authors said.

Because of these economic realities, studies for rare disease therapies are often funded, at least in part, by government or nonprofit entities. The Orphan Drug Act directed the FDA to issue regulations to spur more research in this area and provided funding for orphan product grants. These grants are available for research related to a disease or condition in which no current therapy exists or when the proposed product will be significantly superior to the existing therapy. They can be awarded to clinical studies in any phase of development.

In 2020, the FDA published a review of the agency's orphan drug program in the Orphanet Journal of Rare Diseases to see if it had achieved what Congress intended. Since the program's inception, it has funded more than 700 studies at a cost of more than $420 million. These studies have contributed to more than 70 approvals for rare disease treatments, the review found.

In addition, the authors found that 66 of 85 grants awarded by the program resulted in completed studies. Of those, 46 demonstrated positive study findings and nine reported negative findings. Another 11 demonstrated equivocal findings. In all, seven drugs and two devices were given marketing approval, a number that the study authors considered to be a programmatic success.

"Also remarkable was that the average time from initial funding of these grants to approval was seven years, as it is estimated that it can take more than 15 years to complete all three phases of clinical development and receive marketing approval," they wrote.

"We believe this supports the hypothesis that access to this unique funding mechanism translates to well-designed rare disease studies, allowing these studies to continue development and potentially piquing the interest of other investors to continue supporting the development programs."

Trial Costs

continued from page 1

While this number has fluctuated moderately over the past few years, it's less than half of what it cost per day to run a trial in the 1990s. Tufts believes this figure was reached through the reduction of certain direct costs over time, such as operational-, procedural- and technology-related expenses, in addition to sponsors and CROs asking more of sites without offering more in study grants.

Separating phase 3 from phase 2, the center found that pivotal trials cost about $56,000 per day on average, twice that of phase 2 trials and seven times that of phase 1 trials. They also last far longer, averaging 1,328 days from protocol approval to closeout compared to 1,028 days for phase 2 and just 641 days for phase 1.

Tufts also explored average daily trial costs for specific therapeutic areas, finding that late-stage immunology and respiratory trials are by far the most expensive. By contrast, oncology and cardiovascular disease trials costs the least to run per day.

"Variation around the mean direct daily costs for phase 2 and 3 clinical trials in immunology, cardiovascular, and oncology diseases are relatively high, reflecting wide differences in protocol scope, requirements, and recruitment costs," the report notes.

In addition, today's financial ramifications for missing a day of prescription drug and biologic sales are much less punishing, with sponsors averaging just $800,000 in daily sales (in 2023 dollars) in 2016-2022, a far cry from the Office of Technology Assessment's 1990s-era estimate that sponsors earned an average $4 million per day on prescription sales for drugs and biologics launched in 1992-99.

> "We anticipate that the new and unexpected financial value measures from this study will significantly impact ROI calculations and budget and resource planning decisions."
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> — Ken Getz, executive director, Tufts Center for the Study of Drug Development

CSDD found that daily drug and biologic earnings have steadily declined since the 1990s to the tune of about $100,000 every year. One catalyst for this could be the industry's significant shift toward developing therapies for smaller populations, the center says, with more and more drugs and biologics aimed at rare and genetic diseases hitting the market and facing far stiffer competition as a result.

"The estimated value of a day of delay in prescription drug sales surprised a lot of people. Many assume that the value is always increasing," Getz said. "The unit of measure here is days that a given therapy is generating sales and may be a function of the shorter overall duration that a given therapy has patent protected sales, may be due to increasingly smaller markets (e.g., rare diseases and more narrowly defined patient populations) that these therapies are targeting, and may also reflect intense competition within select crowded markets."

Despite these cutthroat markets, orphan-designated drugs and biologics earn significantly more than non-orphan treatments today when it comes to median daily prescription sales, CSDD reports, with these therapies generating $680,000 per day, 62 percent higher than their non-orphan counterparts, which had median daily sales of $420,000. And since 2000, a greater percentage of products that launched with orphan designations — about 28 percent — eventually hit or surpassed $1 billion in prescription sales, compared to 21 percent of non-orphan therapies.

"Although orphan drugs by definition are targeting smaller relative patient populations, these drugs command much higher relative prices, typically have few if any competitors and may have longer periods of patent protection," Getz noted.

Access the full Tufts CSDD Impact Report here.

Daily Phase 2 and 3 Trial Costs by Therapeutic Area

Top therapeutic areas (Phase II and III trials only)	Mean direct costs per day	Coefficient of variation	Median direct costs per day
Respiratory	$50,351	0.38	$50,032
Immunology	$51,340	0.92	$33,756
Gastroenterology/endocrinology	$36,395	0.77	$32,081
Neurology	$39,437	0.64	$32,601
Dermatology	$41,004	0.74	$30,146
Oncology	$33,365	1.22	$17,039
Cardiovascular	$30,657	1.31	$16.621

Source: Tufts CSDD

Confidential Information

continued from page 1

The article, which discusses the reasons behind the FDA's strong discretion, the ensuing consequences of this discretion and Daval and Kesselheim's legal interpretations, offers a number of recommendations to the agency:

- Address the threat of "reverse FOIA" lawsuits (where companies bar the FDA from disclosing information by suing it for violating the Trade Secrets Act) by amending its own regulations from 1974. "Federal law does not prevent FDA from sharing anything and everything a company considers 'confidential,' but FDA is bound by its own regulations if those regulations say it cannot," they write. "Rescinding a blanket commitment to confidentiality is the necessary first step."

- Think about creating a "notice-and-comment" rule that allows certain information to be shared. This rule could identify what types of information are disclosable and the circumstances under which they can be shared. At the very least, it could enable the immediate sharing of any information that could have a significant impact on public health and safety, such as supply chain and manufacturing capacity-related information or information on the safety and efficacy of marketed drugs

- Work with the Justice Department (DOJ) to define the parameters of the Trade Secrets Act, such as by seeking formal assurance from the DOJ that lays out when the department may pursue enforcement (e.g., an illegal leak by one employee), and when it would not (e.g., when the FDA shares clinical trial results in adherence to a regulation). The agencies could also work together to create a predisclosure review system to ensure that prosecution does not occur

Access the *JAMA* article here.

Viewpoint

continued from page 2

port their long-term strategy, while at the same time benefitting from an immediate capacity lift and jurisdictional expertise to streamline their high-volume contracting for clinical trial agreements (CTA) and participant-facing documents supporting multiyear and multisite clinical studies.

The solution in practice? A quickly deployed SWAT team comprising SMEs for quick-start CTA contracting across multiple sites and geographies immediately impacting day-to-day operations while also bringing enablement expertise. With the contract review and negotiation process, reusable contract "artifacts," such as contract templates and playbooks detailing company risk positions and negotiating tactics, were developed.

The resulting reduction in contracting cycle time meant the company was able to deliver their technology to patients faster, address revenue leaks often associated with delayed site startup and forecast more efficient and predictable trials, all while building a clear roadmap for scalable contracting in the future.

Using Generative AI in Contracting

With generative AI transforming trial contracting, there's a fresh wave of opportunity in the near term to further capture efficiencies and a better stakeholder experience. AI-powered approaches promise to automate routine contract generation and review, analyze historical data to optimize pricing and terms, predict potential bottlenecks and risks, and enhance compliance with regulatory requirements. However, implementing AI-integrated processes starts with process design and rationalization. As an immediate no-regrets step to avoid throwaway costs, prioritize making your knowledge assets, such as templates, clause libraries and contract repositories, AI-ready.

As organizations mature, AI-driven solutions can offer more advanced benefits. Generative AI's language-centric nature makes it ideal for revolutionizing contracting processes, especially in biotech clinical trials. As adoption accelerates,

see **Viewpoint** on page 7

Viewpoint

continued from page 6

companies can benefit from partnering with specialized service providers who invest in cutting-edge AI solutions, rather than making risky fixed investments in this rapidly evolving field.

Allocation of Resources is King

Allocation of resources is everything when it comes to creating an effective contracting ecosystem. Look to align work nature with necessity, capacity, talent and expertise. Integrate technology to enhance speed, efficiency and scalability, tailoring approaches to different contract types, from complex multijurisdictional agreements to lower-risk contracts.

Creating space to think about resourcing and seeking external help can be valuable, not just for legal teams, but for CFOs in biotech. External partners can provide hidden benefits, such as project management, accountability and credibility with the business. They can also help navigate the challenges of implementing and maintaining technology solutions.

As the biotech industry continues to evolve, trial contracting is emerging as a critical strategic lever for driving innovation and financial performance. By treating contracting as a powerful strategic tool rather than a back office function and aligning legal operations with business needs, CFOs can play an outsized role in accelerating time to market, reducing risks and significantly impacting their company's bottom line.

Tech Management

continued from page 3

a trial that's launching with fewer than six different systems, it's a relief from the technology perspective.

The industry has seen massive advances that are fantastic and beneficial, yet the volume of new technology can lead to complications that are challenging for sites. It's hard to maintain the different systems, know every single login and remember what each tool is used for.

Things get even more complicated for sites because the tools and apps will be used differently from trial to trial. We may be using an electronic data capture (EDC) system for one trial, and that same system is your interactive response technology for another trial that uses a different EDC system. Most of these systems also require specific training as well, and more often than not, there is a certificate that the sponsor is unable to access that we need to provide prior to gaining full access to the trial.

There's just so much tech to manage, and while not impossible to keep up with, it adds unnecessary complexity.

It may sound counterintuitive, but to keep up with all the technology, we've adopted more technology. Adopting a clinical trial management system (CTMS) and an eISF system has greatly improved and streamlined our trial organization. Password and link management tools are also fantastic; they can mitigate some of the challenges of having so many different systems across trials and provide a very simple organizational platform to know what apps we're using by trial.

CWM: *What advice would you give sites and sponsors on managing technology?*

AG: Skylight only recently adopted some of the advanced technologies we've been discussing, the big ones being the eISF in late 2022 and CTMS earlier this year.

From a site perspective, I am such a big advocate for bringing on an eISF and CTMS so sites can have more control. Maintaining the same umbrella technology across all studies from the perspective of regulatory, participant and financial management at least gives one aspect of technological consistency. It can be a tremendous amount of work to implement, but sites shouldn't fear technology that they can control; it's a lot easier to manage your own technology than to be handed six different logins for a trial to figure out.

For sponsors, I'd love to see them consistently provide a simple guide of the systems being used, what they're being used for, a link to access them, any training certificates required, and who to contact if you need assistance. A simple table could take a lot of guesswork out for sites.

Beyond that, I'd give the sweeping advice to simplify the number of platforms and leverage more cohesive systems that provide end-to-end solutions and systems that can communicate.

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