Acurian on...

Defying Industry Assumptions with a Disruptive Approach to Solving Patient Enrollment Challenges

Most Patient Recruitment Organizations (PROs) have essentially been doing the same thing for many years. To raise awareness of clinical trial opportunities and encourage enrollment, their basic functions include: trial advertising and marketing communications, site support materials, study websites, and limited metrics tracking.

In this traditional model, patient conversion (the continuum that begins with targeting marketing messages to potential trial participants, and ends with patients actually *enrolling* in the study) is delivered under a fee-for-service and pass-through cost basis. Consequently, sponsors of clinical trials often view PROs as a regrettable spend – a purchase they feel forced to make in light of unexpected enrollment delays, and over which they have little control. They may express frustration that they are basically throwing money at a PRO without any guarantee of results or at least a contract for services *based* on results.

At the same time, clinical trial sponsors and their Contract Research Organizations (CROs) have been attacking current enrollment challenges (such as ever more complex study protocols and greater competition for patients) in the same, non-innovative way. By increasing their research site footprint and/or extending deadlines, they preserve the *appearance* of completing a study on time. Clearly, there is a need for disruptive innovation in this space to look at the challenge through a different lens.

In all of these contexts, the central flaw is that the trial enrollment planning starts with strategies centering on the sites' projected contribution to overall patient enrollment. The research world has changed, yet our industry continues to revere the sites' position on enrollment. **At Acurian, we believe strategic patient enrollment that is founded on patient-first feasibility and backed by the proper contracting context can actually help pharmaceutical companies change the trajectory of their drugs' value.**

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The Impact of Patient-first Feasibility on Costs and Timelines

Acurian's patient-first feasibility combines tens of millions of proprietary patient data points and the sponsor's protocol design to accurately predict how and when patient randomizations will occur, using study-specific enrollment algorithms rather than relying on what the sites *say* they can deliver.

This clearly challenges the usual CRO model of site-first feasibility (i.e., hiring sites to achieve patient yield based on their subjective declaration of enrollment ability). With the latter, sponsors are often paying double for patients: first for the CRO plan, and then for the additive or replacement cost of a PRO or for simply adding more sites and time. Enrollment is the part of the plan that CROs cannot execute consistently and predictably.

Instead, Acurian offers an enrollment solution that recognizes patients as the bedrock of the clinical trial. By going directly to the desired population, and understanding, motivating and supporting them throughout the trial, the entire process becomes much more predictive.

Patient-first feasibility allows us to control the conversation with patients, deliver **enrollment certainty** (the ability to complete enrollment on time, every time), and provide accountable contract terms (in effect, replacing sites with our stated patient commitment). Our insights and expertise in patient profiling lead to the most cost-effective price per patient, as well as greater patient compliance and retention.

Enrollment Feasibility Models

Patient-first feasibility for a clinical trial models the patient's motivation, behavior and eligibility at the source: the patient.

Site-first feasibility, in contrast, models the patient's motivation, behavior and eligibility through the lens of the site's multiple business objectives.

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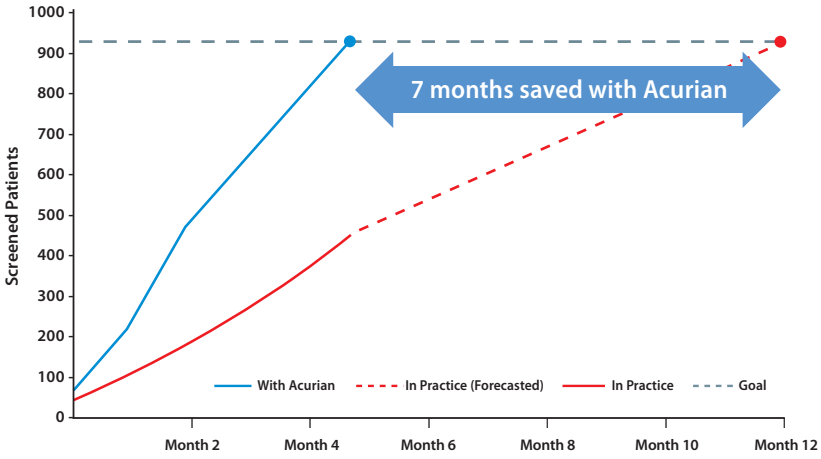
Drawing on our track record of delivering results, Acurian acts as a *lever* to improve nearly all of the operational efficiencies of a trial, *if* patients are placed at the center of it. In a sense, Acurian can be seen as a special kind of CRO, contributing 50-70% of the total patient enrollment, using pinpoint elegance instead of a shotgun approach.

Typically, Acurian shaves three to nine months from pivotal phase III filing timelines, providing cost savings in the hundreds of thousands of dollars and moving sponsors to first in the race to regulatory approval. Moreover, these accelerations are capturing *hundreds of millions* of dollars in patent-protected revenue for companies with the vision to adopt Acurian's disruptive paradigm.



Actual time savings graph from an Acurian project in migraine indication

If this kind of cost-saving, market-moving and ROI-generating disruption is available in the clinical trials industry now, why aren't there more takers? Several misconceptions may cloud sponsors' decision making.

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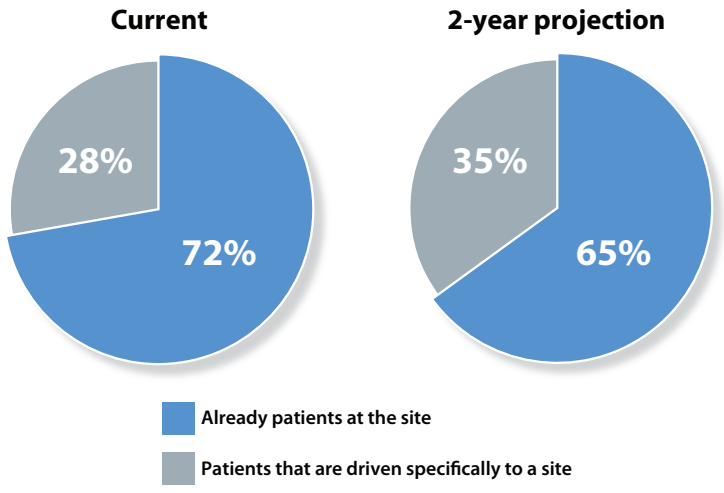
Continued Overreliance on Sites as Proxies for Patients

It is time to recognize that enrollment is no longer the sole province of sites. That is a 20-year-old view that has been weighing sponsors down in a continuous rut of prescribed behavior. Sites are not full proxies for patients, and recent research underscores that sponsors are finally starting to deviate from this belief.

An Industry Standards Report (ISR) titled "The Expanding Web of Clinical Trial Patient Recruitment" showed that clinical trial managers are shifting their thinking, albeit it slowly, toward a recognition that sourcing patients outside the sites' purview is vital to success. The ISR data suggest that at the time of the report, 28% of patients in clinical trials were not active patients at the site. In other words, 72% of the trial participants were sourced from in-practice patients. However, the respondents foresaw that in two years' time, there would be an increase in the proportion of patients that are sourced externally, to 35%.



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The time and expense of adding sites is not a viable solution in many cases, yet sponsors are reluctant to change due to their fear of breaking with tradition. And the general outlook on enlisting outside enrollment support at a later date becomes problematic. Unless you plan for enrollment (patient recruitment) assistance from the beginning of a study, it will always be viewed as an additive expense (or regrettable spend) rather than a replacement for the amount you *would* have spent on more sites or more time allotted for the study.

If you are still setting up a global infrastructure – much of which is for access to patients – and then adding on enrollment costs, it will obviously increase the budget for the study. Acurian's view is that the focus of enrollment assistance should be on providing certainty of time and cost. By keeping patients at the center of the trial and reducing the sites, countries and timeline, the sponsor can reduce other costs that would be included in a CRO bid. Moreover, by limiting the global site footprint, there will be fewer study anomalies.

Cost Comparison of Enrollment Options: Phase III Study for General Osteoarthritis

	Enrollment Options		
Scenario	With Acurian	Extend Enrollment by 74 months (no other changes)	Add 1,178 U.S. sites
Enrollment Duration	25	99	25
Total U.S. Sites	401	401	1,579
Number of Subjects Screened	8,292	8,292	8,292
Randomizations	5,695	5,695	5,695
CRO, Site and Investigator Costs	$76,488,976	$269,075,875	$272,742,868
Acurian	$31,590,306	$0	$0
Grand Total Cost	$108,079,282	$269,075,875	$272,742,868
Incremental Cost	$31,590,306	$192,586,899	$196,253,892

Enrollment Option Cost Drivers

	With Acurian	Without Acurian (Add Time)	Without Acurian (Add Sites)
Project Management	No Change	Increased	Increased
Clinical Trial Document Preparation	No Change	No Change	Increased
Study Conduct	No Change	Increased	Increased
Site Management	No Change	Increased	Increased
Regulatory	No Change	Increased	Increased
Biostatistics	No Change	No Change	No Change
Medical Writing	No Change	No Change	No Change
Data Management	No Change	Increased	Increased
Pass-Through Costs	No Change	No Change	Increased

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Concerns about Transparency and Risk Mitigation

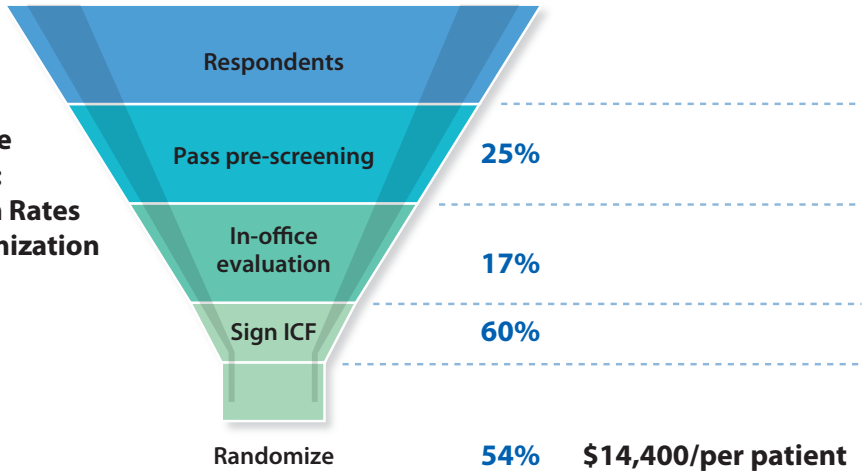
The fortitude to deviate from convention is currently available only from a PRO like Acurian that stands behind its ability to source patients globally, with full financial accountability. Our innovative patient-first model is built on deep understanding, vast knowledge and broad support of clinical patients, and proven over years of development and real-world experience.

Many sponsors won't change their recruitment strategy because the incumbent processes are comfortable – even though they are also wasteful and risky. Yet, pharmaceutical industry history has clearly shown that most studies are late, and most at some point add time or sites. So why is outside enrollment seen as inherently *more* risky?

The answer is, with most PROs, it is impossible for sponsors to gain any visibility into the methodology, processes or metrics being used to support enrollment. These recruitment providers do not give any indication of where or how much patient attrition will occur in the continuum, or where their quoted price is coming from.

The Acurian method of enrollment certainty offers less risk precisely because it is **transparent.** Acurian quantifies the challenges of recruitment up front, by providing per-patient costs and projected rates of attrition throughout the continuum, based on our long experience in central recruitment campaigns and patient relationship-building, and highly accurate and proprietary enrollment feasibility analysis.

Funnel drives the per-patient cost: Sample Attrition Rates through Randomization



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The benefits of leveraging Acurian-driven enrollment *prospectively* as a cost-neutral or cost-positive replacement for sites and countries have been demonstrated through hundreds of cost analyses conducted using third party costing tools. With our results-based pricing contracts across a wide variety of chronic, ambulatory disease trials, we state our ability to deliver, and then we price on it. Accountable, predictable, and efficient, the patient-first approach lessens the sites' administrative burden, provides greater control, and mitigates the risk for *all* parties involved.

Value of Acurian Additive Patients:
Phase III Study for Hypercholesterolemia

	Traditional Strategy	Acurian Strategy	
# of Countries	6	1	**Fewer Countries**
# of Sites	40	35	
Acurian Involvement (Yes or No)	No	Yes	
Recruitment Period	10 Months	6 Months	**Less Time**
Enrollment Rate (Pts/ Site/ Month)	0.506	0.926	
Total Timeline	24.6 months	20.7 Months	
Cost Reductions (direct & indirect)	--	~ $770,000	**Less Money**

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Where Does Patient-First Best Fit?

Therapeutic Focus	Indications
Respiratory	Allergy, asthma, COPD
General Medicine	GERD, gout, IBS, menopause, atopic dermatitis, OIC, uterine fibroids
Neuroscience	RA, OA, migraine, MDD, DPN, pain, LBP, sleep apnea, insomnia
CV/Metabolic	Cholesterol/triglycerides/lipids, hypertension, diabetes, obesity, DFU, gastroparesis

Patient Quality and Dropouts

There has long been a concern that patients who come from third parties are not as qualified or will drop out of a study at a higher rate than those supplied by sites, but this is not substantiated by the data we have seen. The numbers have even been independently verified by statisticians from Acurian's sponsor customers. For example, the sponsor of a four-protocol program for Major Depressive Disorder conducted an independent analysis that determined the rate of response (Montgomery-Asberg Depression Rating Scale [MADRS] total score changes) was similar for both Acurian and non-Acurian patients across all four protocols, and Acurian patients completed treatment at a higher rate than non-Acurian patients across all protocols. Similar results have been documented in other therapeutic areas such as diabetes and pain management.

Embrace Disruption to Succeed

Sponsors should view the right recruitment provider as a strategic investment rather than a regrettable spend. Faced with the direct question, "If I could guarantee you the full complement of patients for your study out of *half* the sites, would you do it," everyone would say "Yes."

Such a disruptive proposition – a contingent of patients comparable to that provided by contracted sites, without the associated cumbersome infrastructure and speculative investment, but *with* patient-first feasibility, risk mitigation and accountability – is available today from Acurian. What are you waiting for?

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