WORLDWIDE CLINICAL TRIALS

5 QUESTIONS TO ASK A PROSPECTIVE CONTRACT RESEARCH ORGANIZATION

AND WHAT THE ANSWERS TELL YOU ABOUT ITS ABILITY TO ACHIEVE YOUR DRUG DEVELOPMENT GOALS

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ASK A WORLDWIDE EXPERT YOUR QUESTION

WORLDWIDE CLINICAL TRIALS

CROs CONSOLIDATE AS R&D EFFICIENCY DECLINES

Raising pressure on drug sponsors to select the right partner

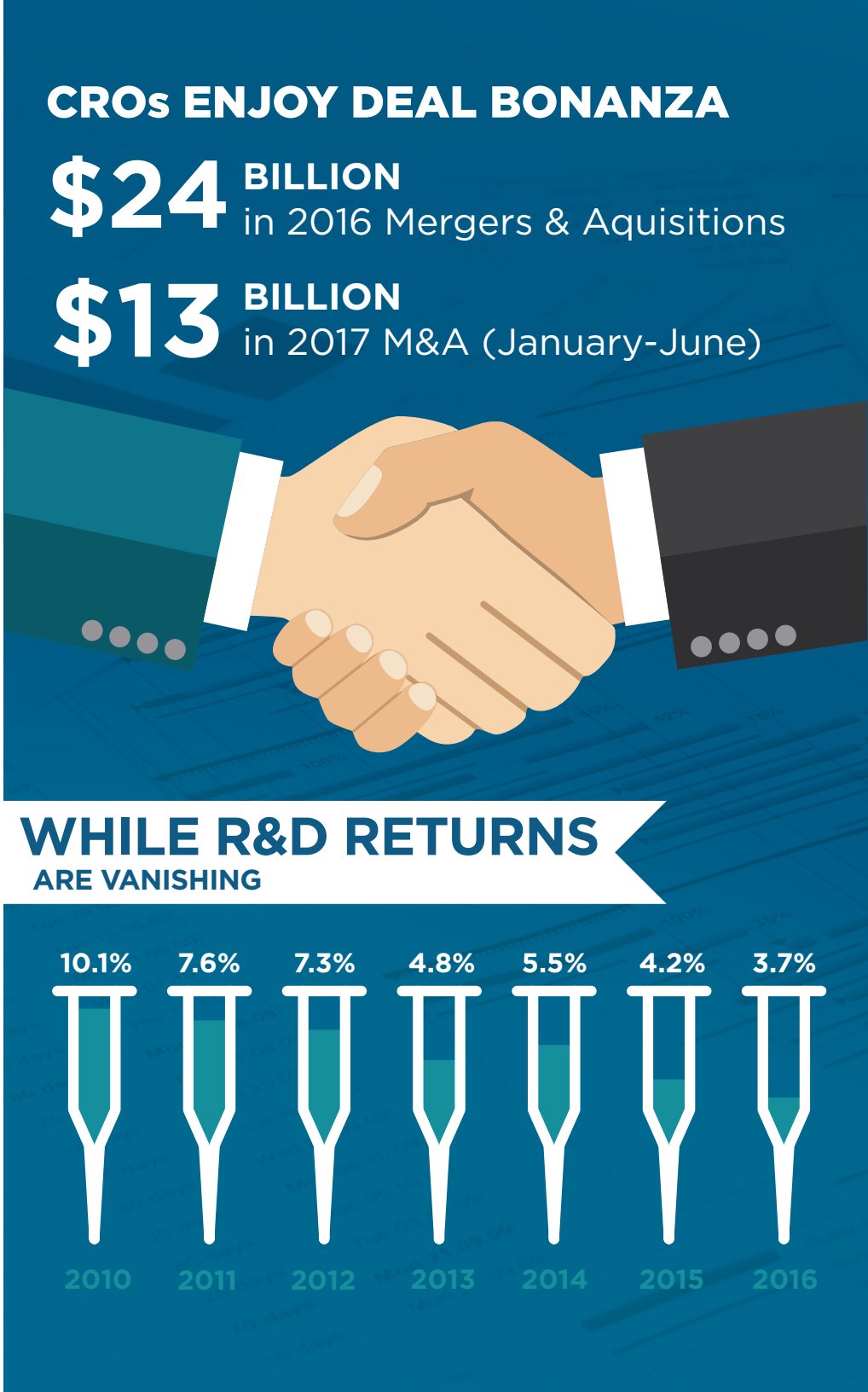
Recent mergers and acquisitions among contract research organizations (CROs) have significantly altered the industry landscape, creating a new class of mega providers while the level of productivity in large pharmaceutical companies continues to decline[1,2]. The combinations at the top end of the CRO industry created three supersized competitors that have the resources and broad suite of capabilities to cater primarily to large pharma. Yet measured by return on investment (defined as the successful approval and launch of new medicines), R&D productivity at the 12 leading biopharma companies is shrinking, down from 10.1% in 2010 to 3.7% in 2016.

This merger activity could be beneficial for CROs categorized as small or midsized, says Jason Monteleone of Pivotal Financial Consulting, LLC. This group of CROs, which includes Worldwide Clinical Trials, "can continue solidifying their status as the partner of choice for small pharma," as both the mega and large sized CROs may not fit small pharma's needs, he adds. In fact, small pharma has outperformed large pharma in recent years, according to research by the Deloitte Center for Health Solutions. Maintaining this levels of productivity within small and midsize pharma companies will require consistent improvements in sponsor-CRO partnerships. To help these relationships get better, this eBook identifies a few key questions that can serve as a starting point. Based in part on a recent CRO quality report from ISR[3], these vital questions can help you select a service provider to deliver results.

> **With complex protocols, nuanced patient phenotypes, and innovative technologies, it's a brave new world for drug R&D.**

Make your molecule a star

While CRO partnership decisions are likely to be multivariate in nature, clinical trial sponsors do have common questions to help drug sponsors select a research partner that can stand out from the crowd and help make your molecule a star.



1. WHAT IS YOUR PLAN TO ACHIEVE OPERATIONAL EXCELLENCE?

Look for a healthy marriage between CRO's science, medicine and clinical trial operations.

Though no industry statistics exist on the number of CRO-sponsor partnerships that end in divorce, a good marriage between the two is certainly needed for achieving operational excellence.

Just as important, however, is the relationship within the CRO among those running operations and those who guide medical decision making. How do people with a process engineering mindset get along with colleagues who arrive at decisions by balancing methodological rigor with medical expertise that combines the art and science of clinical care? If this internal marriage works — if there's open dialogue, collaborative thinking and mutual trust — then the external partnership is more likely to give birth to a successful clinical trial. If not, expect disappointment. Too often today the latter case is the result. The ever-increasing use of contract service providers has had little-to-no impact on accelerating development timelines[5]. Yet there are bright spots. Many small drug sponsors have succeeded in lowering the cost of development and CROs are essential to their operating model. See the sidebar for a cost comparison between small and large companies, and a basic operations checklist.

How do people with a process engineering mindset get along with colleagues who arrive at decisions by balancing methodological rigor with medical expertise to handle the complexities of patient care?

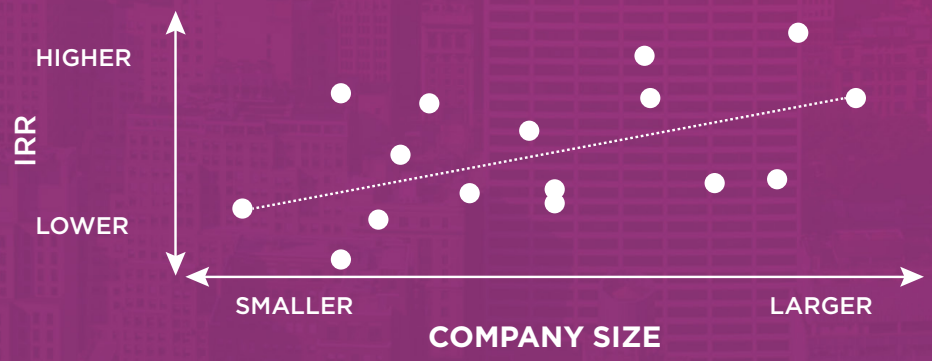
More questions than answers?

Getting beyond the basics with probing questions will help give a true assessment of how the CRO works internally or does not. If the bid defense raises more questions than answers, consider other options. After all, getting cold feet before an engagement is better than trying to rescue a failed marriage when facing an impending drug development milestone.

OPERATIONAL SCORECARD

METRIC	EXCEEDS	MEETS	FAILS
Financially strong and stable			
High quality project management Low turnover of Clinical			
Research Associates Minimizes change orders			
Proactive contingency planning and risk management			
Procedures in place for high data quality			
Responsiveness			

COMPANY SIZE VS. 3 YEAR AVERAGE COST TO DEVELOP AN ASSET



Smaller companies spend less to develop an asset. This chart compares size (measured by 10-year R&D spend) with 3-year average cost per drug asset. Units are omitted to protect anonymity[2].

2. HOW FOCUSED ARE YOU ON MY THERAPY AREA?

Does the CRO have clarifying insights about perplexing diseases?

Both successful CROs and drug sponsors share a commitment to focus on specific therapeutic areas and indications. Biopharma companies that have a lower volatility in therapeutic area make-up of their late-stage development portfolio outperform those that are continually changing the focus of their drug development efforts[2]. The same could be said of CROs: Therapeutic focus is necessary for clinical excellence. Embedded within these focused CRO partners is a depth of knowledge and scientific expertise needed for successful development and commercialization. They offer a better path than CROs that claim superiority across numerous therapy areas, or those that chase hot development trends to meet revenue expectations. The targeted approach has gained importance in recent years. Based on current science, it is now more difficult to find areas of viable unmet clinical need. Many diseases now have first- or second-line treatment options that reduce or eliminate symptoms or the disease itself. In areas where needs remain unmet, for example, Alzheimer's and other Central Nervous System (CNS) disorders, complex and poorly understood underlying biology stymie progress. Trials in CNS are especially hard to design and operationalize. In fact, neurology and psychiatry are two of the least probable diseases to achieve successful approval during Phase 3[7]. CROs must have deep knowledge and expertise if they are to beat the odds in Alzheimer's or other perplexing CNS indications.

Embedded within these focused CRO partners is a depth of knowledge and scientific expertise needed for successful development and commercialization.

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ASK A WORLDWIDE EXPERT YOUR QUESTION

CLINICAL TRIALS SUFFER FROM HIGH COMPLEXITY & CHALLENGING DESIGN

Total median procedures per protocol increased from

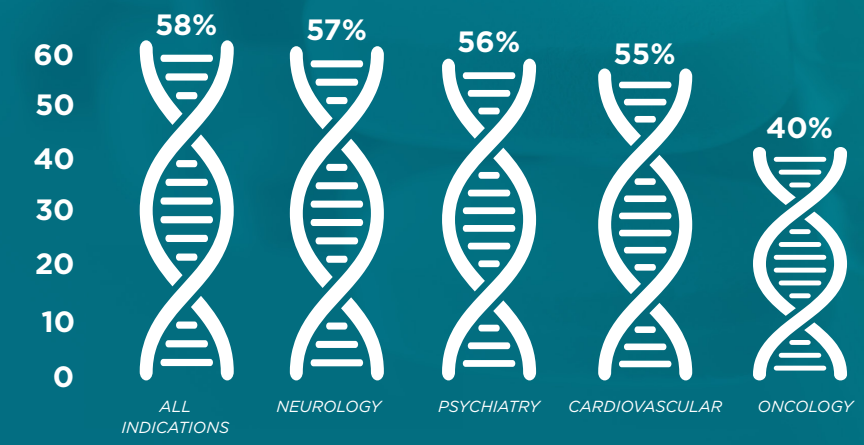
105.9 2000-2003

166.6 2008-2011

according to Tufts Center for the Study of Drug Development[6].

PROBABILITY OF PHASE 3 SUCCESS

Phase 3 transition success rates by disease area. Categories are listed from highest to lowest based on the probability of transitioning from Phase II to NDA/BLA filing[8].



3. HOW DO YOU BUILD INVESTIGATOR & SITE RELATIONSHIPS?

Remaining patient centric while not forgetting the needs of the clinical sites.

In the increasingly patient-centric approach to drug development, patients are informed collaborators whose participation is core to the overall success of trials[9]. While this trend is encouraging, it remains crucial for sponsors and CROs to balance patient-focused activities with increased site engagement[10]. There are three essential steps to building investigator and site relationships:

1. **Follow structured processes**
2. **Be consistent with interaction and engagement**
3. **Have purposeful communication**

A structured relationship begins with a solicitation meeting where a mutual confidential disclosure agreement (CDA) can be put in place, followed by a face-to-face meeting by study coordinators to agree upon lines of communication and potential roadblocks. High- level processes are set for the following, to ensure collaboration at all levels:

- **Pre-award input: Encourage a site's input on protocols, beyond just issuing a survey.**
- **Site identification: Set a clear path to becoming preferred sites and know how to become a favored sponsor.**
- **Issue escalation: State how will this be handled to accommodate the needs of multiple stakeholders.**
- **Communication: Frequency is key but purpose matters too. Ensure that expected responses or changes are clear.**

By communicating with purpose, engaging with sites throughout the study and operating with clear processes, sponsors and CROs ensure trials remain patient centric while making it easier for sites to conduct studies enhancing site commitment and improve data quality.

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PATIENT CENTRICITY REMAINS TOP OF MIND

126

GLOBAL OPINION LEADERS

in preclinical and clinical research at biopharma companies were surveyed about patient centricity[11].

87%

OF RESPONDENTS
Are discussing patient centric approaches to clinical development

with half of the surveyed companies expecting to enhance patient-centric approaches to clinical develpment within:

1-3 YEARS

4. DOES YOUR GLOBAL FOOTPRINT MAKE SENSE FOR MY STUDY?

Claims of a global presence may not be enough to meet enrollment goals with trial sensitivity.

The reasons for conducting clinical trials in emerging regions are well established. For the past decade, lower operational costs, more treatment-naïve patients, and quality research capacity have attracted drug sponsors. However, recent regulatory concerns and the potential for lost continuity in clinical care have led to a decline in study initiation within several of these countries, notably India and China. Still, at least one region — Central and Eastern Europe — retains the positive qualities of a developing market with fewer complications.

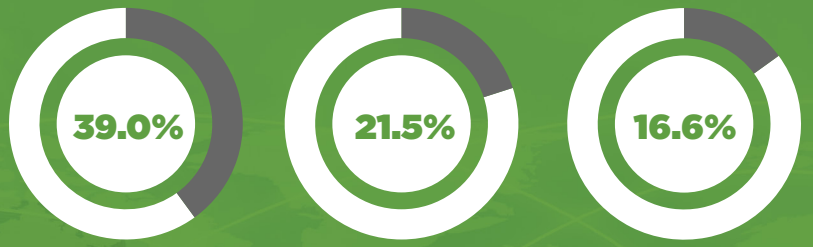
Most CROs claim to have a global presence. But what does that mean for your study? Just as CROs succeed by focusing on specific therapeutic areas, they work best when they have a history in countries that make sense for your study. Can it access the sites and populations that will enroll in your trial? If so, does it understand local cultures, regulatory requirements and local standard practices of medicine to enable predictable study initiation and execution?

In Eastern Europe, for example, extra care must be taken to ensure the allocation of trial funding achieves appropriate balance between hospitals and investigators. By achieving a proper partitioning of funds, allocations will be available to cover space for site, monitors to work, record retention facilities, Internet access, etc. In these cases, sponsors must rely on investigators to secure these resources from the hospital.

A CRO's global footprint may look good on a map, but if it navigates research by global positioning system (GPS) rather than hard won experience it is bound to step on toes.

Central and Eastern Europe: Attractive R&D Markets with Quality Clinical Infrastructure

% OF CLINICAL INVESTIGATOR INSPECTIONS WITH NO DEFICIENCIES



FDA's Clinical Investigator Inspections list shows Central and Eastern European compliance and data quality are not inferior to Western Europe[13].

OVERALL CLINICAL TRIAL COSTS

The cost of conducting clinical research in Russia is less than half the cost of the US (manpower, rental, IT & operational costs)[14]

Russia	$$$$$$$$$$	0.40
Argentina	$$$$$$$$$$$$	0.48
China	$$$$$$$$$$$$$	0.52
India	$$$$$$$$$$$$$$	0.56
Brazil	$$$$$$$$$$$$$$$	0.61
Czech Republic	$$$$$$$$$$$$$$$	0.61
Hungary	$$$$$$$$$$$$$$$$	0.68
Poland	$$$$$$$$$$$$$$$$$	0.77
Israel	$$$$$$$$$$$$$$$$$$$	0.86
Taiwan	$$$$$$$$$$$$$$$$$$$$	0.90
South Africa	$$$$$$$$$$$$$$$$$$$$$	0.99
US	$$$$$$$$$$$$$$$$$$$$$$	1.00
UK	$$$$$$$$$$$$$$$$$$$$$$$	1.09
Singapore	$$$$$$$$$$$$$$$$$$$$$$$$	1.19
Ireland	$$$$$$$$$$$$$$$$$$$$$$$$$	1.25
Germany	$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	1.58

5. HOW CAN YOU DELIVER VALUE AND INNOVATION?

Taking a strategic approach to drug development pays dividends.

Despite questions about the blockbuster business model, drugs with over $1 billion in annual sales still carry a certain cache[15, 16]. However, many R&D executives have another number in mind: $2.6 billion. That is the cost to develop and win marketing approval for a new drug, according to the Tufts Center for the Study of Drug Development[17]. Other analyses present different estimates, but industry costs are often shown to be outpacing revenues. Protocol design trends are one of the prime drivers of rising costs. A typical Phase III protocol now entails an average of 167 procedures, 60% more than at the start of the millennium[6]. With this growth in mind, it makes sense to engage with a CRO that takes a strategic approach to trial design. One that engages early with patients, providers, and payers and has a robust process for risk management will bring valuable dividends.

Big Ideas from Small Players

In this risk-averse industry innovation is coming from small companies and the CROs that support them. In 9 of the last 10 years, more than 60% of new drugs approved originated from smaller biopharma companies[18]. The CROs that are helping to deliver this innovation bring operational excellence, unique therapeutic focus, deep relationships with investigators and sites, and a global footprint that helps sponsors achieve value in every engagement. Smarter protocols, risk-based and metric-based oversight, and strategic partnerships are are needed to ensure advances in drug development continue coming to market.[19]

> **One that engages early with patients, providers, and payers will bring valuable dividends.**

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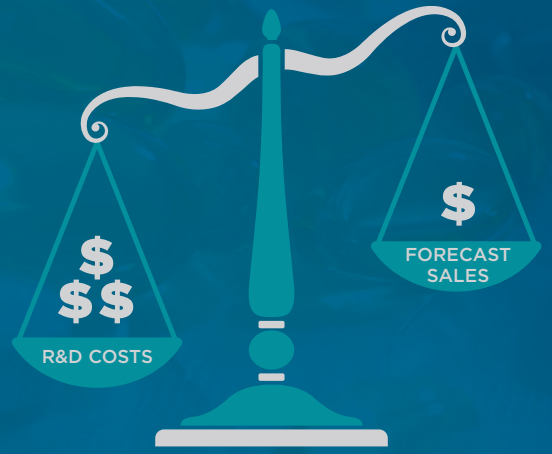
THE URGENT NEED FOR VALUE

DRUG DEVELOPMENT COSTS ROSE 145% FROM 2000 TO 2013

FACTORS LEADING TO HIGHER CLINICAL TRIAL COSTS

- **STUDY SIZE**
- **COMPLEXITY**
- **GREATER FOCUS ON CHRONIC & DEGENERATIVE DISEASE**
- **PROTOCOL DESIGN**



THE CURE FOR THE COMMON CRO

From early phase and bioanalytical sciences through late phase and post-approval, Worldwide Clinical Trials combines proactive insight and rigorous operations with a never-satisfied approach to delivering world-class, full-service drug development services. We seek out the perfect study group in the perfect region of the world. If the sample population isn't yielding as expected, we change course, without compromising data quality. When something isn't working, we flex to meet your needs, while staying true to best practices. We innovate. We do whatever it takes to perform your trial successfully. In compliance. On time, and on budget.

WE CONSISTENTLY WIN INDUSTRY ACCOLADES

- 2017 CRO Leadership Award Winner (Life Science Leader, 12 out of 15 categories)
- 2017 #1 Contract Research Provider (Nice Insight Survey)
- 2017 Clinical Partnership of the Year (Pharma Intelligence)
- Finalist - Best Contract Research Organization 2016 (Scrip Awards)

Because we're changing the way the world experiences CROs in the best possible way.

WORLDWIDE CLINICAL TRIALS

CRO LEADERSHIP AWARDS 2017

This program recognized performance in five core categories (capabilities, compatibility, expertise, quality and reliability) across three groups – "Big Pharma," "Small Pharma," and "Overall." Worldwide came away a winner in 12 of the 15 categories.

Worldwide Clinical Trials was honored as a finalist in the prestigious 2016 Scrip Awards. Selected in the "Best Contract Research Organization – Full Service Providers" category,

CORPORATE LiveWire Healthcare& Life Sciences AWARDS 2016

Corporate LiveWire recognized Worldwide as "Best in Neuroscience Therapeutics" in its 2016 Healthcare & Life Sciences Awards, which recognize the pinnacle of business achievement and organizations that have made a difference in patient lives.

This prestigious award recognizes Dr. Michael Murphy's exceptional contributions and his consistent history of service and dedication to the clinical research industry throughout his career.

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