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ELIMINATING PATIENT 'DISRUPTION'

PERSONALIZED MEDICINE

ADVANCED THERAPIES: OPERATIONAL IMPACT

WASHINGTON REPORT
Data Integrity Lapse Spotlights Wider Actions

EU REPORT
Fighting the Drug-Pricing Link to New Innovation

CLOSING THOUGHT
Patient Experience and Drug Development

New Wrinkle in Outsourcing Views

LISA HENDERSON
Editor-in-Chief

The Avoca Group has published the results of its 2018 Industry Report "Clinical Outsourcing Spend and Key Relationships Measures." In addition, it submitted an article based on the results, which is featured in this issue on page 10. The results themselves are interesting enough, but dive into the "Provocative Ideas" presented by Avoca COO Dennis Salotti for some additional food for thought.

In that section, Salotti suggests that individual respondents' industry tenure and exposure may be becoming more apparent in these results, specific to the key outsourcing health indicators—relationship, quality, delivery, and value. The survey found that respondents working in the industry for less than 10 years were more generous in their satisfaction scores vs. those in industry greater than 10 years. Salotti makes very good observations here. For one, clinical outsourcing has greatly evolved from its origins more than 30 years ago, with significant jumps in just the past 10 years. As Salotti points out, "The trend in outsourced clinical development spend remains consistent with previous waves of research and is forecasted to remain stable through 2021 at around 60% of the total clinical development budget." And he lays down Tufts CSDD stats for an industry representing $8.5 billion in 2008, now at over $30 billion.

What that all means is that outsourcing now is more the norm, and many professionals travel seamlessly between pharma and CRO. Many in industry less than 10 years may not be aware there were whole conferences devoted to the very subject of this report, the relationship and partnering attributes between the two stakeholders.

Salotti also brings in the generational cohort, referencing surveys of millennials and their outlooks related to the workplace—all workplaces, not specific to clinical trials. And this is not an eye roll to millennials but adds to what could offer potential insight to the underlying Avoca responses. The beginning of the millennial generation is 1981—literally, the oldest are turning 40. I recently had my own eye-opening experience around generational differences on 9/11 when my sons, born in 2002, noted they felt removed from the remembrances because it was outside of their own personal experience. It's not an insignificant leap to accept that a person's basic experiences and perceptions are affected by generalizable factors such as generation. Salotti did note that these potential underlying perceptions weren't examined separately in the surveys, and all require further discussion and study.

The usual caveat, while we focus on the issues and topics on our website throughout the year, the next time we revisit the clinical operations and outsourcing relationships piece in focused issues is next year. In April, we will feature "Does ClinOps Need a Makeover?" driven by recent observations that SOPs are driving the development bus and, thus, does the function need a fresh new look? Then next September, the CRO and Sponsor Relationships issue, where we will visit some of these initiatives in play by CROs to address the smaller biopharma needs, as well as trends on the outsourcing front. Meanwhile, stay tuned for our Regulatory Update issue in December, and please participate in our Salary Survey, with results heading your way in January.

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WASHINGTON REPORT

NOVARTIS DATA MANIPULATION CASE SPOTLIGHTS WIDER CONCERNS, ACTIONS

Public confidence in the safety and efficacy of medical products—particularly innovative cellular and gene therapies—requires sponsors to provide complete and accurate information in all regulatory submissions. Evidence that Novartis manipulated certain preclinical data in developing its $2 million breakthrough therapy Zolgensma—and did not disclose the problem until after FDA approved the product—produced a strong, public rebuke from FDA and an outcry from policymakers. FDA officials said they may pursue civil or criminal charges, and Congressional leaders demanded that Novartis provide a full accounting of its actions.

In a harsh statement issued in early August, Peter Marks, director of the Center for Biologics Evaluation and Research (CBER), emphasized the importance of FDA having confidence in all tests and data submitted by sponsors, particularly to support the rapid development and approval of innovative therapies that benefit from accelerated pathways.

Two decades ago, the death of young Jesse Gelsinger in a gene therapy clinical trial brought development of the field to a halt, and regulators and investigators fear that safety issues raised by faulty studies or incomplete submissions could stymie continued progress in advancing cutting-edge medicines. The law requires submission of "truthful, complete and accurate data" in order for FDA to be able to protect the public health, Marks asserted.

In publicizing this situation, FDA aimed to send a clear warning to biopharma companies that data manipulation is a serious offense, and that data quality is critical for accelerated approvals, as well as more routine regulatory actions. Marks said that Zolgensma would remain on the market, as the questionable test results involved early animal studies and not results of clinical trials, and thus did not compromise safety or efficacy for this potentially life-saving treatment. Yet, he acknowledged that if reviewers had been aware of the erroneous test data at Novartis' AveXis unit, CBER probably would have delayed approval.

Particularly troubling is that the company evidently knew of the data errors as early as last March but did not launch a formal investigation until May, and did not reveal these issues until June. But that was after the agency approved Zolgensma on May 24 based on evidence that it dramatically improved the health of infants suffering from the most severe form of the neurodegenerative disease spinal muscular atrophy (SMA). However, an FDA follow-up inspection in late July of AveXis' San Diego control test lab found evidence that management failed to thoroughly review unexplained discrepancies in potency assays, had incomplete records, and failed to follow quality control and test procedures. These events led to the dismissal of AveXis scientists and Novartis restructuring its relationship with AveXis to increase oversight.

Reliability of results

Ensuring the reliability of clinical data is an ongoing priority for FDA, as seen in repeated citations in warning letters of inadequate and inaccurate records at clinical sites in violation of good clinical practices (GCPs). Regulators addressed these concerns and outlined appropriate responses at a workshop in October 2018 on "Data Integrity in Global Clinical Trials" sponsored by FDA and the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

International standards for data integrity also are being examined as part of a project to update policies to ensure human subjection protection and reliability of trial results by the International Council for Harmonization (ICH). A new guideline (ICH E8) is under development to revise requirements for assuring data quality, along with policies governing clinical trial design, data sources, and the protection of trial participants.

Sponsors say they would like to see clearer guidance on what specific information they should provide regulators when they uncover discrepancies in preclinical and clinical reports during drug development. These issues will be discussed further at an FDA public meeting on Oct. 31 to review the draft E8 proposal and gather comments from stakeholders.

FDA has similar concerns about ensuring data integrity in drug manufacturing, as well as product development. A warning letter sent in August to Chinese over-the-counter drug manufacturer, Ningbo Huize Commodity Co., cites egregious data integrity lapses. FDA banned import of the company's products following a plant inspection where local staffers provided FDA investigators with documents that were clearly falsified, including batch production and control records for multiple drugs.

In highlighting this enforcement action, FDA Acting Commissioner Ned Sharpless stated that efforts to "prevent, uncover, and combat data integrity lapses" is a continuing commitment for the agency. FDA requires sponsors to submit complete and accurate information in applications and, in turn, is providing additional resources to address data integrity issues through increased global inspections, updated guidance, and additional staff training.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

8/28/19 Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products

9/5/19 Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older

9/23/19 Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment

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EU REPORT

FIGHTING HIGH PRICES FOR INNOVATIVE DRUGS WITH NHS GENERIC PRODUCTION

As the arguments over drug pricing and patient access continue to rage around Europe and North America, UK socialists have raised the temperature further—on the brink of national elections—with a strongly-worded plan for reining in profit-driven drug companies.

"We will redesign the system to serve public health—not private wealth—using compulsory licensing to secure generic versions of patented medicines," said its leader, Jeremy Corbyn—who is formally Leader of Her Majesty's Most Loyal Opposition, in the arcane terminology of the UK parliament, which means he is the theoretical default alternative UK prime minister if Boris Johnson's government falls.

"We'll tell the drug companies that if they want public research funding, then they'll have to make their drugs affordable for all," Corbyn went on. And his other headline-grabber was: "We will create a new publicly owned generic drugs manufacturer to supply cheaper medicines to our NHS, saving our health service money and saving lives."

The bounce-back from drug firms was immediate. Dr Richard Torbett, executive director of commercial policy at the Association of the British Pharmaceutical Industry, said compulsory licensing, "would completely undermine the system for developing new medicines. It would send a hugely negative signal to British scientists and would discourage research in a country that wants to be a leader in innovation." A patent lawyer, Alex Robinson, described it as, "a sure-fire route to protracted, repeated litigation and increased costs" since each compulsory licence would require proof that current provision is not, "reasonable terms" and agreement on, "reasonable remuneration" for the patent holder.

The concept of a nationally-owned generic manufacturer has also come under fire—on grounds of logic as much as ideology. Once a product's patent runs out, there is effectively a free-for-all where companies can in any case produce the medication if they so wish, said Frances Weetman, a centrist UK politician. It would, "likely make no difference to the cost of drugs" as, "the industry already benefits from vast market competition internationally." Plus it would cost a lot to set up, "Little benefit for vast expense," said Weetman. Robinson made a similar point: "The government would need its own manufacturing facilities, compliant with all regulatory requirements, and able to produce and distribute output sufficient for UK demand. This would clearly require either (a) vast capital expenditure on facilities ,which we do not presently have; or (b) expropriation of currently-existing privately-owned manufacturing facilities. And that's before we consider staffing, or funding."

But for all the weaknesses that can be pointed to in the Labor agenda (and they are many—take, for example, the following, "The most sustainable way to keep drug prices down is through competition among generic suppliers."), the disaffection that underlies the bold initiative is genuine, and cannot, or should not, be ignored.

The immediate trigger for the Labor interest is the controversial non-availability of Orkambi in England. Corbyn expressed admiration for a nine-year-old sufferer from cystic fibrosis campaigning for access to the drug—imported as a generic, if necessary. For three years, the U.S. drug company Vertex Pharmaceuticals, "has pushed for the NHS to pay the highest possible price for their drug Orkambi (lumacaftor-ivacaftor). In that time, despite a desperate campaign for an agreement, hundreds of eligible patients have died without access to the drug," says the Labor party manifesto for health.

It goes on to argue that the case of Orkambi is, "just the latest example of the failings of the current pharmaceutical innovation model, where patients are held hostage by a system in which innovation is inextricably tied to private ownership." The manifesto endorses and rehearses the familiar criticism that, "patent-backed monopolies allow drug companies to charge whatever the market will bear, holding lives to ransom until they get their price."

The Orkambi saga leaves the industry on the back foot in debates of this nature, and the discomfort of industry spokespeople is palpable. Torbett at ABPI prefaced his warning about the negative implications of compulsory licensing with the observation, "The situation on Orkambi is rare, but it is clearly unacceptable, and a solution needs to be found for patients and their families."

And as long as no solutions have been found—for Orkambi or for others in the constantly-growing group of expensive innovations that attract high public profile but no reimbursement—the industry will remain on the back foot. Which will expose it to attacks that may not be entirely logical or coherent, but manage to gain wide public support.

— Peter O'Donnell

EMA NOTES

AGENCIES ALIGN ON DECISIONS FOR NEW MEDICINES

A study was conducted of a joint EMA/FDA analysis comparing decisions on 107 new medicine applications from 2014-2016. Findings show that the agencies are aligned in more than 90% of marketing authorization decisions for new medicines.

The study also looked at applications for which the agencies had differing outcomes in terms of type of approval and indication. The most common reason for diverging decisions at the two agencies were differences in conclusions about efficacy. Differences in clinical data submitted in support of an application were the second-most common root of divergent FDA and EMA decisions.

The article, with study results, is available through open access in *Clinical Pharmacology & Therapeutics*. View here: http://bit.ly/2ngmJO9

Q&A

ALZHEIMER'S RESEARCH FINDS NEW BEGINNINGS

The field of Alzheimer's disease (AD) poses significant opportunity but has been faced with big challenges and massive late-phase clinical trial failures. Despite subsequent setbacks in the field, emerging biopharmaceutical companies are still pursuing AD therapies with new science, and different preclinical and clinical trial models. In this interview, Dr. Daniel Alkon, president and chief science officer at Neurotrope, discusses novel approaches to AD therapy development.

Moe Alsumidaie: Why is Alzheimer's disease an area of great challenge with many trial failures?

Daniel Alkon: When Alois Alzheimer discovered the disease around 1906, it didn't have any traction. In 1984, two scientists identified a protein called amyloid-beta. When that happened,everyone thought,"Oh, this will be a real breakthrough because we now know what key protein is involved. And it was involved in what are called amyloid plaques and tau tangles, neurofibrillary tangles,which are the pathologic hallmarks.

The main approach, neuro-pharmacologic approach, is where researchers tried to develop drugs to address other deficits that people had thought attended those pathologic deposits, such as the loss of cholinergic neurons, which contribute to memory and attention deficits. This worked to the point where we developed drugs that provided mild symptomatic relief, but did not treat the disease. So, the industry started to focus on getting rid of amyloid-beta buildup, as they believed the disease was caused by that protein.

There have been many approaches to try to reduce amyloid-beta. One is to use animal antibodies to combine with and eliminate amyloid-beta; another involves activating enzymes in the brain to degrade amyloid-beta, and another is to inhibit enzymes in the brain that help form A-Beta, such as inhibitors of beta-secretase; none of these approaches worked. Many scientists had thought that amyloid plaque and tau tangles were destroying brain neurons and synapses; this theory was also disproven.

MA: What have you discovered is the main contributor to AD?

DA: I worked on memory at the NIH and then at the Rockefeller Neuroscience Institute for 15 years, and we implicated certain key molecular pathways that were responsible for memory formation. In memory formation, we found that we could demonstrate with electron microscopy the formation of new synapses. Once we understood that and the pathology that had been acquired with human brain samples, we hypothesized that we could facilitate not only memory formation but also the formation of synapses, which might be a regenerative or restorative approach to AD.

That motivated us to work on clinical trials, first with a compassionate use trial with patients suffering from advanced AD. We generated successful results, hence, we went to a Phase II trial, and we published the results recently in the *Journal of Alzheimer's Disease*.

Alexander Neumeister: What is your hypothesis?

DA: Our hypothesis is that since we saw an improvement in patients who underwent the compassionate use trial, we pursued a larger number of patients to see if we could achieve similar results. Results from that study demonstrate clear signals, including not only a reduction in degradation, but also a reversal in memory loss and an improvement in their conventional psychometric measurements. Even one month post-study completion, and after all treatment had been stopped, results were consistent with a new and constructed wiring. These findings have encouraged us to continue development with this hypothesis.

MA: What did other researchers miss in their animal models?

DA: I think a lot of the industry was misled by some of the animal models that they used. For example, there was one double transgenic amyloid precursor protein (APP) model that the industry used. The APP model makes a huge amount of amyloid, so much amyloid that it acts like a tumor occupying space in the animal's brain. So, if there is a reduction in that amyloid and it's not so huge anymore, the animal tends to get better. But that's not what happens in AD; we tend to observe a gradual build-up of much less amyloid.

Daniel Alkon

MA: Why did you target patients with advanced AD?

DA: While we have every reason to believe that we can treat much milder cases and even prevention, we chose patients with advanced AD because we saw benefits in the compassionate use patients, which were very advanced. And it's because the industry basically has abandoned that niche and we wanted to see whether we could undertake that challenge.

MA: What challenges did you experience with recruiting and retaining patients with advanced AD?

DA: Patients with advanced AD are a challenge to recruit. But, fortunately, we had 27 sites with principal investigators at each site and a dedicated team of researchers. We were pleasantly surprised that we could recruit the patients, even though they were advanced based on their caregivers making the decision, and we believe that we saw such good recruitment figures because of our relationship with our investigators and their relationship with their patients and caregivers. We also believe what

Q&A

contributed to this success was the hope of reversing AD with these patients; we saw very few dropouts, and we think that was fueled by the hope that our medical product could improve those patients' lives. For instance, in the compassionate use trial, one patient who has a familial gene for early onset AD (by the time she was 31 or so), and couldn't speak, swallow, or move at the beginning of the trial, saw a significant improvement in speech, movement, and her livelihood. That story got around, and the story fueled recruitment and retention.

— Moe Alsumidaie, MBA, MSF, is a thought leader and expert in the application of business analytics toward clinical trials, and an Editorial Advisory Board member for and regular contributor to Applied Clinical Trials.

Alex Neumeister is Head of Medical Affairs at CliniBiz and specializes in protocol design, drug safety, and clinical trial management.

NEWS NOTES

FDA GAINS APPROVAL TO REVAMP NEW DRUG REVIEW OPERATIONS

After months of planning and explaining, Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), finally gained approval for broad changes in its process and procedures for evaluating and approving new drugs. In the works for nearly two years, this effort to modernize and reorganize CDER's Office of New Drugs (OND) establishes additional new drug review offices and divisions more aligned to assess therapies for interrelated diseases and conditions. In addition, new administrative offices aim to better manage policy development and program management.

Under the new structure, an OND deputy director for clinical operations will oversee eight (up from six) offices with 27 review divisions (vs. 19 divisions now). The aim is to better align staff expertise with more defined therapeutic areas, while also reducing workloads so that scientists and physicians can better respond to changes in biomedical science. The new Office of Oncologic Diseases expands to five review divisions, while neuroscience is separate from cardiology. There's a new division for rare diseases and medical genetics, and a new Office of Nonprescription Drugs, but with limited staff pending Congressional approval of a new user fee program in this area. The clinical review offices will work more closely with relevant divisions of clinical pharmacology/toxicology from CDER's Office of Translational Sciences (OTS). And all these groups will be linked to a new Office of Drug Evaluation Sciences with divisions for clinical outcomes assessments and biomarker qualification and biomedical informatics.

Novartis and Microsoft strike AI deal

Early this month, Novartis found the Novartis AI innovation lab and selected Microsoft as its strategic AI and data-science partner for this effort. The new lab aims to bolster Novartis AI capabilities from research through commercialization and help accelerate the discovery and development of transformative medicines for patients worldwide.

As part of the collaboration, Novartis and Microsoft have committed to a multi-year R&D effort. The strategic alliance will focus on two core objectives:

■ AI empowerment. The lab will attempt to bring the power of AI to the desktop of every Novartis associate. By bringing together vast amounts of Novartis datasets with Microsoft's advanced AI solutions, the lab will focus on creating new AI models and applications that can augment associates' capabilities to take on the next wave of challenges in medicine.

■ AI exploration. The lab will use AI to tackle some of the hardest computational challenges within life sciences, starting with generative chemistry, image segmentation, analysis for smart and personalized delivery of therapies, and optimization of cell and gene therapies at scale.

Partnering on telemedicine study

Science 37, a virtual clinical trials company, and the Keck School of Medicine of the University of Southern California (USC) established a partnership that will support the execution of a $3.4 million study funded by the National Institutes of Health (NIH)—the largest telemedicine-based dermatology study ever funded by the organization. It will attempt to determine whether telemedicine can deliver care that is equivalent to being seen in-person for patients with eczema.

Elligo receives grant to study RWD

Elligo Health Research has been given a grant from FDA for a follow-on project to extend the value of common data harmonization in the generation of clinical evidence from real-world data (RWD) to support regulatory use. This grant will enable Elligo to explore methodology and use cases to further goals of the 21st Century Cures Act related to facilitating data sharing. Achievements from the first phase of this project include mappings of multiple data models (OMOP, PCORnet, i2b2, and Sentinel) to the BRIDG Model (an HL7, CDISC, and ISO standard), a reference data model, and terminology bindings.

Evotec, Takeda form discovery pact

Evotec and Takeda Pharmaceutical Company Limited have entered into a strategic, multi-year drug discovery collaboration designed to establish at least five drug discovery programs with the goal of Evotec delivering clinical candidates for Takeda to pursue into clinical development.

Targeting digital therapeutics for MS

Mental health technology company Happify Health has signed an agreement with Sanofi to advance the application of digital therapeutics to address key comorbidities for individuals living with multiple sclerosis, including depression and anxiety.

— Staff and wire reports

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Begin with the End in Mind is one of management guru Stephen Covey's *7 Habits of Highly Effective People*. This tenet, when applied to clinical trials, reminds us to consider the whole system of start-up, including EDC, budgets, and contracts when trying to improve clinical trial payments.

Budgeting and contracting are the earliest site-facing trial activities—and as sponsors move toward adaptive designs, the budget and payment schedules have become even more intertwined and complicated. It is at this early stage, when a budget is being developed, contracts are negotiated, and an EDC system is set up, that sponsors and all stakeholders should be collaborating and focusing on the full financial lifecycle of the trial to streamline operations. This holistic approach will improve cycle time and allow sites to be paid within the desired 30-day terms.

Key take-aways:

- Understand how all start-up activities are interconnected
- Learn how to streamline budgeting and contracting to improve payments
- Review sponsor challenges and successes through a compelling case study

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For technical questions about this webinar,
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Industry Report on Outsourcing Spend, Models, and Measures

Dennis Salotti

A look at the findings from Avoca Group's 2018 industry research survey on clinical outsourcing.

CRO/ SPONSOR

Each year, The Avoca Group invites clinical trial professionals from sponsor and provider organizations to participate in research on prescient industry topics and to provide key benchmarks on the current state of clinical outsourcing. For this year's report, Avoca analyzed data from approximately 300 web survey responses representing over 200 global individual sponsor and provider organizations.

Sponsor respondents (128) represented a balanced distribution across small (sales <$500 million), mid-sized (sales $500 million–$10 billion), and large (sales >$10 billion) biopharmaceutical firms. Nearly two-thirds of respondents were in clinical development/operations, quality assurance/compliance, and executive management functions. Small and mid-sized CROs (sales <$50 million and $50-$500 million, respectively) were represented most prominently (81%), with large CROs (sales >$500 million) and non-CRO clinical service providers rounding out the sample (see Figure 1 on next page).

Current and future trends in clinical outsourcing spend

Similar to the findings from Avoca's 2017 research,[13] current and forecasted levels of outsourcing spend in clinical development remain stable. In aggregate, sponsors indicate they outsourced 61% of clinical development work and anticipate remaining around this level through 2021 (see Figure 2 on next page). Continued growth overall in R&D spending[1] along with increasing costs of drug development[2] will drive spend in outsourced clinical development, despite the relative proportion allocated to outsourced spend remaining flat.

When asked to further allocate their clinical outsourcing spend in relative proportions to full-service and functional service provider (FSP) types, in aggregate, sponsors indicated a relatively even split in both current and three-year estimates. Breaking out smaller (sales <$2 billion) from the top 50 biopharmas (sales >$2 billion), smaller sponsors currently allocate more of their outsourced clinical development spend to full-service providers compared with their larger counterparts that maintain a relatively balanced allocation to full service and FSPs (see Figure 3 on page 12). In three years, this difference is anticipated to narrow to a more balanced allocation across models, regardless of company size.

Providers indicated that a larger proportion of their revenue comes from FSP than from full-service arrangements (2018: FSP, 57%; full service, 43%). And, like sponsors, they reported stability through 2021 in these relative allocations by model (2021: FSP, 53%; full service, 47%). Launch announcements at the 2019 DIA Annual Meeting by two of the top 10 CROs[3,4] for FSP offerings, and identification of functional service solutions among the 2019 Key Strategic Initiatives by a third CRO,[5] may indicate continued growth in the demand for FSP either alone or as part of mixed-model outsourcing approaches.

In order to understand what's driving model selection, we examined the key health indicators for outsourcing, both in aggregate and by outsourcing model primarily employed, while also examining other cohorts such as sponsor company size and respondent length of experience.

Key outsourcing health indicators: Relationship, quality, delivery, value

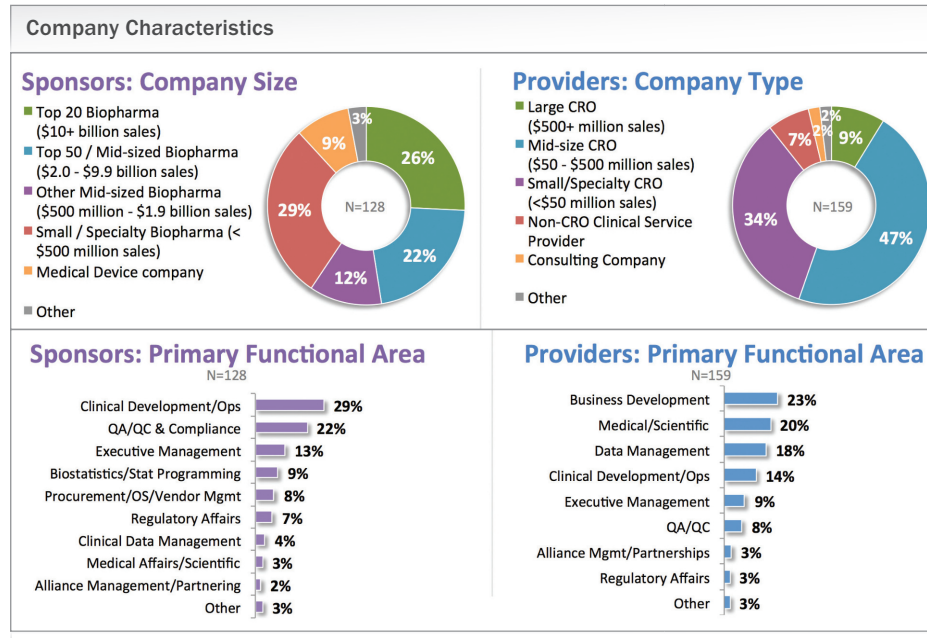
There remains a persistent gap in perceptions of satisfaction between sponsors and providers across several key health indicators for outsourcing, including satisfaction with the relationship, overall work, quality, and value delivered/received. Results from 2018 represent the wid-

est gap recorded within each attribute (see Figure 4 on next page). To refine our understanding of factors that may impact these ratings, we evaluated several subgroups and identified three key comparisons where perceptions differed: company size, outsourcing model primarily employed, and respondent tenure in the biopharma industry.

Company size

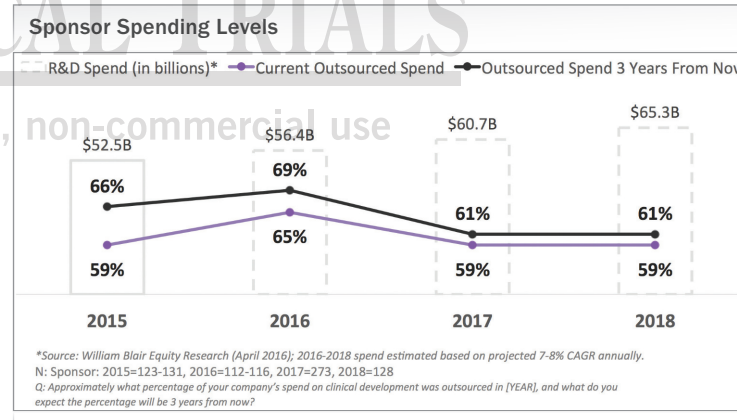
When sponsor companies with less than $2 billion in sales (smaller biopharma) were compared to those with sales exceeding $2 billion (larger biopharma), we found slightly lesser mean satisfaction scores across all dimensions. On further breakout to examine the smallest biopharma category (those representing <$500 million in sales), considerably more neutral views of providers for quality, overall work, and value as compared to all other larger organizations were found (see Figure 5 on next page).

Increased funding into the biotherapeutics sector[6]—and a growing trend among large CROs to focus on biotech with the formation of targeted divisions or acquisitions[7-9]—may address a commonly vocalized perception of smaller biopharma receiving lesser levels of service compared to their larger peers. We may see ratings of satisfaction with providers begin to align across sponsors of all sizes in future studies.



Source: The Avoca Group

Figure 1. Survey respondent breakdown and focus areas.



Source: The Avoca Group

Figure 2. The proportion of outsourced clinical development spend.

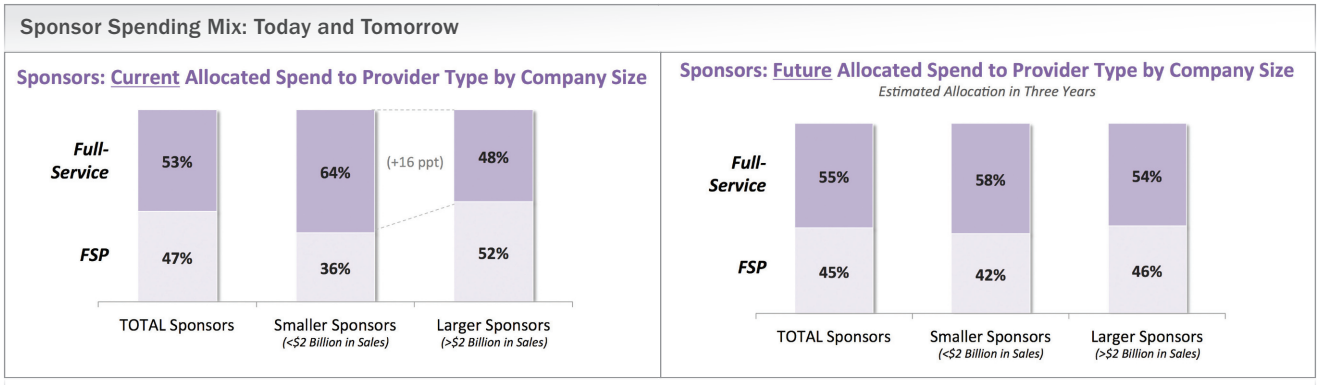
Outsourcing model

The superiority of one model over another in terms of delivering execution, quality, and value back to the sponsor organization is a frequent debate in the clinical outsourcing community. Using the model-specific spend data captured in this research to define cohorts, we compared models across Avoca's four key clinical outsourcing health indicators to examine the influence of model selection on relationships, quality, overall work, and value. We assigned sponsors to either a primarily full-service or primarily FSP outsourcing model based on a minimum usage of 60% for either model as identified in their response and, using these balanced group assignments, found that there was no difference in how sponsors perceived their relationships: FSP and full-service paradigms both yielded fairly high (3.8 out of 5) ratings of satisfaction. Slight differences emerged for overall work, quality, and value where FSP was given slightly more favorable responses than full-service (see Figure 6 on page 14). This model-specific assessment of satisfaction requires further study and longitudinal monitoring to understand if a trend is emerging in favorability of one model to another.

Tenure in industry

Perhaps the most intriguing differences appeared when we compared sponsor respondents' perception of satisfaction to their length of time working in the biopharma industry. Using 10 years of service as the cut-point between groups, professionals with 10 or more years of experience in industry expressed much more neutral levels of satisfaction with quality, overall work, and value, as compared to their lesser experienced peers, who had higher levels of satisfaction (see Figure 7 on page 14).

When we resist the urge to leap to an assumption that these less critical views are a function of naiveté from lesser experience, a few provocative ideas come to mind—all of which require further discussion and study.



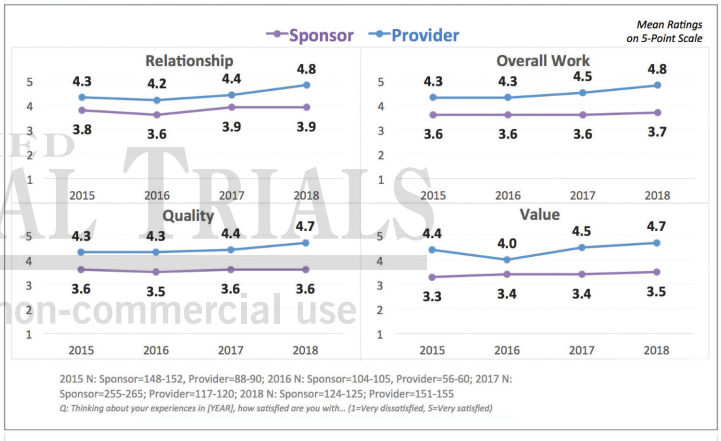
Source: The Avoca Group

Figure 3. The allocation of clinical outsourcing spend by company size and outsourcing model (side-by-side).

Provocative idea 1

In recent years (10 or less), entrants to the clinical trials industry are less likely to know an operating model other than one involving considerable amounts of outsourcing. Their comparative frame of reference may differ from that of longtime veterans of clinical research and development.

In 2008, the Tufts Center for the Study of Drug Development (CSDD) estimated the total market size for contract clinical services at approximately $8.5 billion. Nearly 10 years later, market sizing estimates put the contract clinical service industry at over $30 billion. Using these dollars as a surrogate for the volume and prevalence of outsourcing, it is plausible that many clinical trial professionals with less than 10 years of experience have known no other model than one with heavy reliance on outsourced activities. Many professionals that are relatively early in their careers may not carry a "when we did it in-house" context. Without an intrinsic frame of reference from direct personal experience, these next-generation professionals may fundamentally differ in how they perceive the quality, value, and delivery of outsourced clinical trial services—and may, in the absence of conscious or unconscious biases, carry a mindset free from barriers to effective partnering and oversight.



Source: The Avoca Group

Figure 4. The trends in overall assessment of relationship health among sponsors and providers.

Provocative idea 2

Newer entrants into the clinical trials sponsor workforce are more likely to have worked for a CRO and, therefore, may have greater appreciation for their CRO counterparts than those without that experience.

Data from Tufts CSDD[10] illustrate the impact that growth in the CRO market has had on employment demographics across the pharma industry. Headcounts from major CROs outpace those of major sponsors as far back as 2010, as sponsors strive to trade fixed for variable costs of labor through headcount reductions and concurrent upscaling of outsourcing activity.[11]

With the continued growth in outsourcing activities and productivity pressures on sponsors, it is reasonable to as-

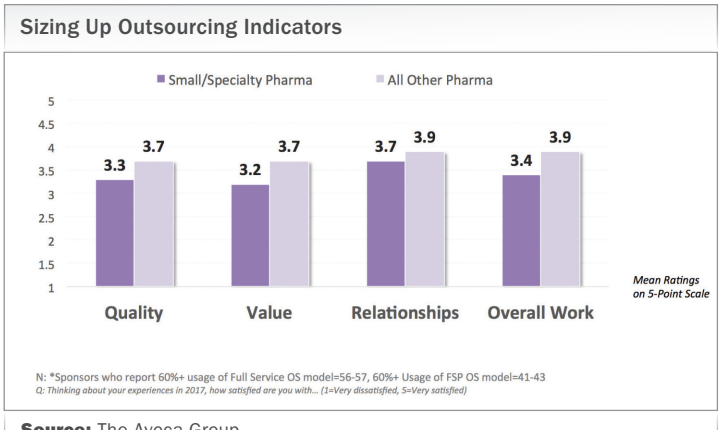


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Figure 5. Comparing satisfaction scores by category of small biopharma versus larger organizations.

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sume that this trend is biasing talent pools at sponsor firms toward a higher prevalence of individuals who have "walked in the shoes" of their clinical service provider counterparts.

Should this phenomenon hold true (it was not studied as part of this research), greater levels of understanding of how providers function would positively influence key attributes of effective outsourcing relationships such as communication, expectation setting, and issue resolution—all of which lead to improved scoring on topline measures of outsourcing health, such as those we observed.

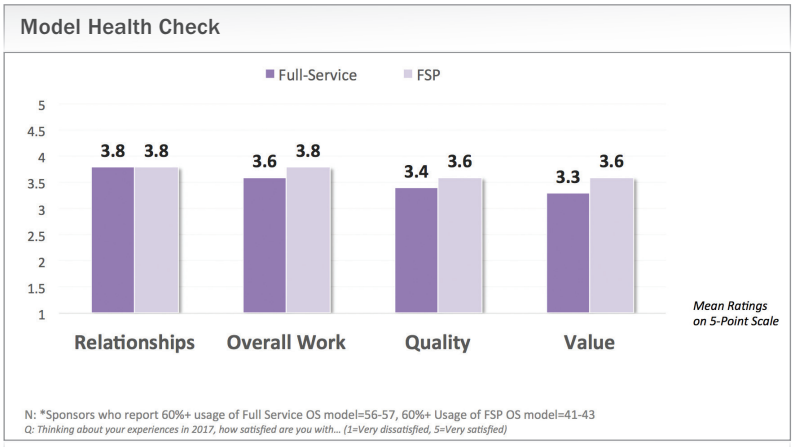
Provocative idea 3

Those earlier in their careers may—as a function of their generational cohort—carry materially different perspectives on risk, quality, innovation, technology, and the workplace than generational cohorts preceding them.

At the risk of being labeled a generational relativist, the difference in perceptions by tenure in industry could indicate the beginnings of a broader shift in perceptions brought about by differences in generational cohorts within the current workforce.

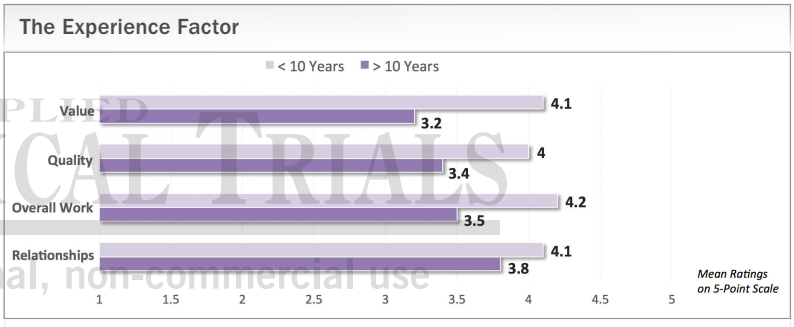
A 2017 study[12] of 8,000 millennials (ages 18–34 at the time) conducted by the research software company Qualtrics and venture firm Accel found:

- 43% of millennials see technology as a double-edged sword and fear it may someday make their role obsolete.
- 43% express desire for a more fulfilling job as a reason to change jobs.
- 51% (double the proportion of Gen Xers and boomers) indicate concern around not having the right skills to succeed in their workplace.



Source: The Avoca Group

Figure 6. The overall assessment by sponsors of outsourcing relationship health from the two outsourcing models primarily used.



Source: The Avoca Group

Figure 7. Comparing perceptions of satisfaction among sponsor professionals with less or more than 10 years of industry service.

This begs the question of how these and other perceptions, perspectives, and desires in this cohort of up-and-coming clinical trial professionals will impact the clinical trials industry and whether we are taking appropriate steps to maximize our opportunities to make them successful.

Considering the vastly different perspectives on, and relationships to, things like data, technology, career, and risk appetite, it isn't too far a leap to assume that these perspectives may be influencing views on clinical outsourcing and potentially other aspects of job performance and job satisfaction among the <10-year experience cohorts.

Conclusion

The trend in outsourced clinical development spend remains consistent with previous waves of research and is forecasted to remain stable through 2021 at around 60% of the total clinical development budget. Similarly, trends in perceptions of satisfaction across key dimensions of clinical outsourcing health appear to be static with a prevalent gap between sponsors and providers, particularly between providers and small biopharma. Tenure in industry—and perhaps generational cohort—also appears to surface interesting differences in perception, though the underlying reasons require further study.

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Eliminating 'Disruption' for Patients in Clinical Trials

Rebecca Kush, John Potthoff

Exploring new ways to smooth the path toward better participation for patients and other research and healthcare stakeholders.

Disruption refers to a"disturbance or problems which interrupt an event, activity, or process"[1] and typically connotes a negative reaction. However, it became a positive buzzword in the technology industry in the late 1990s with *The Innovator's Dilemma*, a book by Clayton Christensen. He introduced disruption as a means for small companies with limited resources to anticipate the future and successfully compete in the marketplace against larger, established companies.[2]

This concept of disruption became used so widely that it prompted Christensen to publish an article in *Harvard Business Review* in 2015 to clarify what he meant by this word.[3] By this time, however, others were using the term and adding their own interpretations to encourage innovative thinking. For example, it was around 2010 that a biopharmaceutical industry leader's term (DPharma) spawned an annual conference, DPharm: Disruptive Innovation, which is organized "to truly challenge conventional methods of conducting clinical trials to address rising costs, protracted time to market, and a heavy patient and investigator burden."[4]

Athena Health also soon got behind the disruption theme. Derek Hedges, Athena Health's senior vice president of business development, wrote in 2012: "I want to tell you about one of the coolest ideas to emerge from Athena Health in years. … Last summer we kicked off our first More Disruption Please (MDP) conference [to bring together leaders] to overthrow established approaches to healthcare delivery so we can make it better, cheaper, and more accountable to the physicians and patients we all serve. It was a smash hit."[5]

These are just two examples demonstrating a general agreement in our industry that new approaches to healthcare and clinical research were (and still are) critical necessities. For these approaches to succeed, collaboration will be key, as well as building better bridges between healthcare and research to pave the way for learning health systems and accelerate learning health cycles.

This was the theme of the Bridging Clinical Research & Clinical Health Care Collaborative in March.[6] Disruption of old processes by new technologies may be a positive concept and may stimulate innovation; however, we must acknowledge that disruption is not what patients seek, especially when considering their healthcare, their well-being, and their livelihood. This point has been discussed multiple times by patient advocates and was made vividly clear again at the Bridging Collaborative by a keynote speaker, an expert in clinical research, who spoke of his circuitous experiences assisting his own daughter through this complicated and disruptive maze when she was diagnosed with a brain tumor.

This article discusses why disruption is occurring and the approaches that must be taken to eliminate this disruption for patients and other stakeholders and smooth the path toward better participation.

Clinical research disruption experienced

The prevalence of disruption and the difficulties it causes potential research participants resonated with one of the authors of this article upon learning that his barber had been diagnosed with prostate cancer. Despite him having found a potential opportunity for his barber at the esteemed MD Anderson Cancer Center in Houston, the barber was unable to take advantage of this study as a care option because it required him to drive 200 miles from his home multiple times, which would have not only disrupted his schedule but his family life and his means of providing income for his family.

Similarly, in a *Scientific American* article entitled "Out of Reach," David Freedman contends that most patients never have the opportunity to participate in lifesaving drug trials due to "barriers at community hospitals," while the most common reason for trials being stopped prematurely or delayed is insufficient rate of patient accrual.[7] To help alleviate these barriers for patients, Freedman states that the burden on community physicians to conduct such research must be reduced.

Another negative disruption for patients stems from the increasingly more complicated clinical research protocols, which are significantly adding to the number of procedures and data points required per study. While it is understandable that a research sponsor would want to get the most out of a costly clinical trial, few would disagree that this can lead to more negative patient disruption.

When we consider the concept of disruption from the physician and investigative site perspective, it is clear the introduction of new technologies into clinical research has been a learning experience. While innovations were rapidly occurring in laboratories with gene sequencing and computer-based modeling for drug design, these studies in the 1990s were largely paper-based at the sites; regulatory submissions were delivered to the FDA in semi trucks.

When we started collecting data electronically, this was initially called remote data entry—implying that the data was central to the sponsor or CRO while sites and patients were remote. Changing the name to electronic data capture (EDC) did not change the paradigm in that these tools were developed more with data managers and monitors in mind instead of site personnel or patients. The common belief was that they would save significant time and money and would thus be good disruptors and innovative.

However, while these tools have indeed enabled faster access to the data and faster database lock, personnel at sites have indicated that EDC does not save them time. In fact, EDC adds burden and takes time away from patient care. Study managers often must enter the same data into the medical record, the EDC tool, and sometimes into another clinical trial management system. Similarly, physicians and their staff have frequently complained that the use of electronic health records (EHRs) adds burden to their busy days.

Patient advocates and research study patients have told stories of similar duplicated data entry—such as having to write down their blood glucose measurements in paper diaries while the same measurements are automatically collected by their glucometers. Unfortunately, patient-facing digital technologies are not yet widely accepted and implemented by major biopharmaceutical companies, although there is great interest in them.[8]

A number of surveys conducted through TransCelerate BioPharma Inc. indicate that there is support for the potential value of these patient-facing technologies in clinical research, but challenges remain before such tools will be widely adopted. Ironically, opportunities cited included improving patient experience, engagement, and compliance while barriers cited include user (i.e., patient) burden and willingness. Unnecessary burden to investigative sites or to patients in research studies could be seen as a negative disruption, and this has historically been one of the main reasons physicians decide not to participate in clinical research.

New approaches to less disruption

Although certain technologies have been negatively disruptive, true innovation provides opportunities to improve research from the perspective of the physician and patient so as not to increase their burden.

Patient advocates and others interested in ensuring the success of research and the value emanating from clinical trials have succeeded in reaching an increasingly large audience, including FDA, research sponsors (biopharmaceutical companies and CROs) and academic research organizations. Their message is important for our industry: patient centricity, including patients in the planning process for research studies, and ensuring that patients receive summary results from the research in which they participate. There are now a number of groups and venues for discussing research as a care option and patient-centered research.

> Technology must be patient-centric while also accommodating the site's workflow in order to be effective.

Technology, which many have turned to as an answer, must be patient-centric while also accommodating the site's workflow in order to be effective. Too often, technology is not interoperable, or it requires data to be entered multiple times. In these cases, technology becomes another burden, not a solution.

There is growing promise that new patient-facing technologies are addressing the barriers and issues currently blocking their widespread adoption and acceptance. Litmus Health, which released its real-world data (RWD) platform earlier this year, has been focused on technology that ensures that all data is collected, stored, and analyzed in "an immutable, trackable and auditable way," according to Samuel Volchenboum, MD, PhD, the company's chief medical officer.[9] He has also stated that "real innovation and contributions to clinical research are going to be centered on how we collect, standardize, and harmonize different kinds of data."[10]

A systems approach to clinical research

The industry has long suffered from solutions such as EDC that solve one problem at a time. An integrated system is necessary to realize breakthrough innovation in the biopharmaceutical industry. Without disrupting patients, this integrated approach should include:

- Patient recruitment, with patients and physicians identified and interest assessed in advance.
- Study setup and data collection that leverage data standards from the start and a physician-focused and patient-centric workflow.
- Collection of true eSource by study managers, eliminating transcription and minimizing the need for mapping downstream for FDA requirements (CDISC eSubmission).
- Study management information, graphics, and met-

rics that are automatically generated in real-time from eSource data, including financials.
- Facilitated study leadership and governance through real-time medical monitoring, regulatory compliance, and robust, HIPAA-compliant communications.

Mary Tobin, PhD, chief strategy officer of the Alliance for Clinical Research Excellence and Safety (ACRES), supports the systems approach to research. In an interview prior to the Bridging Collaborative conference, Tobin explained, "The interconnected nature of clinical research itself has become more apparent. This has been seen in calls to break down functional silos, for taking a systems approach, and aligning various stakeholder interests—'a critical underpinning for bridging healthcare and research.'"[11]

The innovative disruption of research and healthcare without disrupting patients' lives will mean embracing changes that are frightening for those who conduct or oversee regulated research. However, the FDA is encouraging such changes and is not intentionally creating barriers. In fact, at the Bridging Collaborative, Milena Lolic, MD, lead medical officer for professional affairs and stakeholder engagement, Office of the Director, Center for Drug Evaluation and Research (CDER), spoke about how to measure what matters most to patients when they participate in clinical research.

Former FDA Commissioner Scott Gottlieb, MD, also has supported positive disruption. "Unfortunately, we've seen a continued reluctance to adopt innovative approaches among sponsors and clinical research organizations. In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive, but disruptive, changes that certain innovations can enable."[12]

Similarly, Ken Skodacek, with the FDA's Center for Device Regulation and Health, has signaled his support, agreeing to facilitate roundtable discussions at the Bridging Collaborative on "Using Digital Technologies in Clinical Trials: FDA's Support for the Use of Digital Technology Tools" and "Developing Clinical Evidence to Support Innovative Medical Devices: Looking Beyond Regulatory Hurdles."[13]

Indeed, the industry is finally beginning to adopt (rather than pilot) patient-facing digital technology. Volchenboum stated, "Pharma all feel like they are late to the game, but they are all similarly late. Everybody has waited for somebody else to come out in front and do it … and now we're starting to see this real rise of trials using this type of technology."[14]

The easier we can make it for physicians and patients to participate in research, the more we can all learn. Most patients are seeking the latest and greatest treatments, are willing to participate in research if given such a care option, and believe in sharing their data responsibly for the greater good. Putting the patient at the center means making research a positive and worthwhile experience.

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Operational Complexity in Cell and Gene Therapy Trials

Erin Finot

As advanced therapy technology and manufacturing evolve, there are three key operational challenges to address unique to these products.

PERSONALIZED MEDICINE

Advanced therapies (ATs) such as cell therapy, gene therapy, and tissue engineering represent a groundbreaking force in medicine and research. Whereas traditional therapies may use small molecule chemical or biologic products to treat disease, ATs use cells with specifically modified DNA or RNA components to systemically control a disease, replace an aberrant gene, or repair defective tissue. These cellular investigational products have the potential to cure a disease. It is this potential of eliminating disease that could make ATs so revolutionary. At their core, ATs are the result of researchers harnessing the building blocks of life to improve the quality of human lives.

Although less than two dozen ATs are approved by FDA so far,[1] the pipeline to develop these therapies is rapidly growing, targeting therapeutic areas such as genetic disorders, cardiovascular disease, and infectious disease. Currently, however, the majority of ATs focus on oncology, as the unmet need remains high in this area and the rates of most cancers are increasing (see Figure 1 on next page).

As global head of immuno-oncology at IQVIA Biotech, I am heavily invested in helping our customers navigate the operational complexities that arise when designing and running clinical trials for ATs. Three leading challenges specific to AT trials include identifying and selecting the most capable sites, navigating the additional regulatory requirements, and juggling the logistical demands of manufacturing of the investigational cellular product and also handling complex biospecimens.

Site selection

For most clinical trials, the initial stage of the study is notoriously challenging due to the intense planning, robust site selection, and timely site activation required. But clinical trials for ATs come with additional requirements that make the site selection process even more difficult and more critical to trial success.

Since cell and gene therapy trials require integration and coordination with numerous disciplines within the institution (e.g., any combination of the medical or hematological or treating department; a leukapheresis center to isolate the white blood cells; a cell therapy laboratory; an investigational pharmacy; an in-patient treating facility; and outpatient clinics), the number of contributing departments alone presents a difficulty. To address this complexity, we advise customers to invest additional time during qualification and initiation visits to confirm that the sites are fully capable and prepared to handle adoptive cell or gene therapy studies.

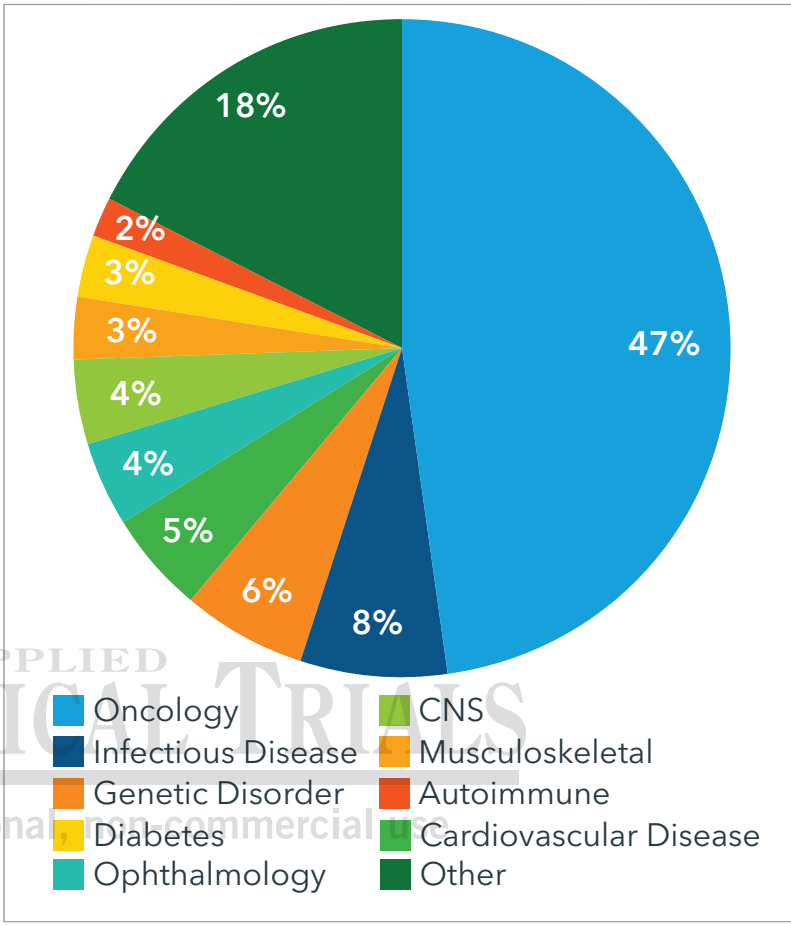
Each of these departments will require a visit and assessment of capabilities, and sometimes contract research organizations (CROs) engaged to conduct the trials need to speak directly with a multidisciplinary investigator team during site selection. This extra time investment during site selection and activation ensures that the sites have the requisite equipment and processes, appropriate handling knowledge, and trained staff and expertise.

To aid site identification and selection activity, biotech companies can start by considering Foundation for the Accreditation of Cellular Therapies (FACT)-accredited institutions. These AT-capable global sites have already established their capabilities and infrastructure and have met recognized accreditation standards. Evaluation of these sites to confirm that they meet all capabilities and possess the appropriate expertise for the specific AT trial is still requisite; however, targeting some of these sites is one component to creating a robust site identification strategy. To supplement this strategy, interroga-

tion of a CRO partner's site database or evaluation of a subscription database on site and trial performance may yield additional sites to consider. Lastly, investigator relationships, networks, and thought-leader support are paramount to concluding a comprehensive site identification strategy.

Currently, facilities needed to conduct AT trials are highly specialized and are, therefore, restricted to a limited pool of medical and academic institutions. In the future, one goal is to increase the number of locations where patients in need can access these therapies. To achieve this, locations such as privately owned sites or community-based facilities may partner with a larger organization and work together to navigate the various in-patient, out-patient, and specific protocol requirements. Alternatively, as the AT field continues to advance, AT trials may become less complex, thereby reducing some barriers to participation by community centers. Although significant progress is being made, there are still monumental challenges to overcome before this will be commonplace. Before we can expand treatment opportunities and localities, AT manufacturing, standardization, and the time and cost of administration must be optimized to meet patient needs in a variety of settings.

ATs Under Development and On the Market



Source: IQVIA European Thought Leadership analysis; IQVIA Pipeline Intelligence 08/2018

Figure 1. While efforts in advanced therapies are targeting many disease areas, the greatest focus is oncology.

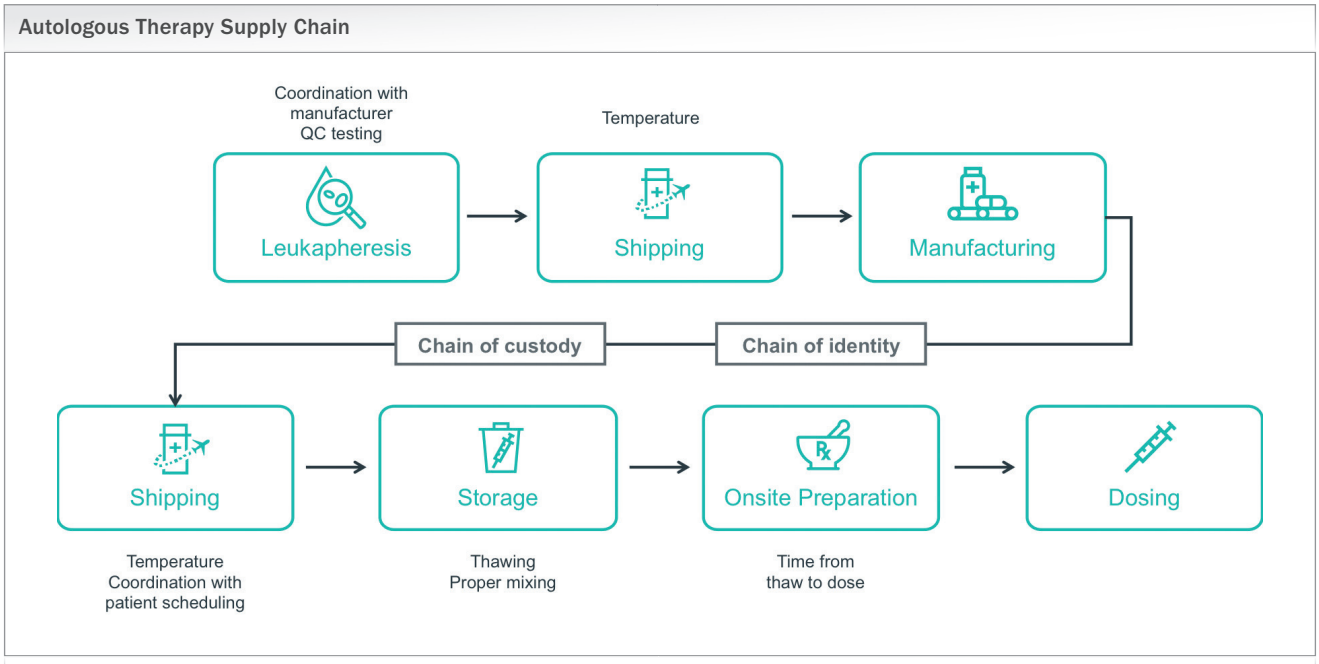
Regulatory requirements

After selecting a suitable site, an AT trial must receive approval of the investigational product and intended clinical trial protocol from country-level regulators and site-level committees and boards before enrolling any patients. In addition to fulfilling global International Conference Harmonization Good Clinical Practice (GCP) guidelines[2] and receiving standard requisite approvals (e.g., FDA and institutional review board [IRB] clearance), AT trials are often evaluated by specialized committees or local standards. These reviews differ from country to country but are intended to ensure oversight of the scientific property or genetic material used within the AT, to ensure adequate handling of the AT, or to uphold public safety.

Because of the genetic nature of ATs, they are often subject to strict, country-specific guidelines. For example, studies using viral vectors such as lentivirus and adenovirus are subject to genetically modified organism (GMO) directives in the European Union (EU) but not in the U.S.[3,4] Raw materials or local testing performed during development of the AT may be accepted in one region, but not in another (e.g., donor cell testing and documentation or non-GMP reagents), and this represents global variability to the AT technology itself. Biotech companies planning an AT clinical trial should ensure their technology is accepted in all countries in which they plan to operate, otherwise they will risk having to increase the amount of capital they invest to render the technology acceptable for the trial. Therefore, global regulatory planning and landscape understanding is critical to the success of AT development and running an AT trial.

Furthermore, there are regulatory checkpoints in place to ensure adequate handling of the AT material and to protect patient, clinician, and public safety. In the U.S., institutional biosafety committees (IBCs) review most AT studies at an institutional level, while in Europe, studies must meet the standards of the advanced therapy medicinal product (ATMP) directive[5] and may need to be reviewed by national GMO experts. In lay terms, IBCs are similar to IRBs, though instead of reviewing research ethics, their core objective is to ensure adequate and safe handling of the AT material. IBCs operate under U.S. National Institutes of Health (NIH) Guidelines—and it should be mentioned that many, but not all ATs, must have an IBC review in the U.S.

Similarly, in Europe, GMO requirements are intended to ensure adequate and safe handling of the AT material, but there may be national variability depending on the precise GMO classification and



Source: Finot

Figure 2. The complex pre-dosing process for an autologous advanced therapy drug.

environmental risk determination. Each of these steps can lengthen start-up times as compared to non-AT studies, but are important to ensure that proper handling procedures are implemented, and patient or public safety is protected.

Due to the broad variability of requirements globally for AT studies, as well as the growing comfort with ATs, it is important to evaluate each AT trial based on the specific therapy, scientific construct, and potential manufacturing process against a contemporaneous global and local regulatory landscape to determine what additional expert reviews must be met before enrolling patients. The regulatory landscape has changed for ATs recently with the 2018 NIH Statement and April 2019 Guidelines,[6,7] and it will likely continue to change (e.g., EU CTR 536/2014). Because of this, it is important for biotech companies to understand the current state and anticipate the future state, both of which may impact their AT development goals.

Logistics

AT clinical trials have tremendous logistical complexities, from the manufacturing supply chain of the AT product itself to the frequency of biospecimen collection during the study. Biospecimen collection in AT studies seemingly occurs around-the-clock, to ensure safety, evaluate kinetics, determine function or efficacy, and collect exploratory samples. Biotech companies must have a detailed protocol laid out that dictates the timing, quantity, and type of biospecimens needed for the trial, as well as a plan for how to transport and store and assay them.

Autologous therapies, which are AT therapies manufactured from a patient's own cells, are manufactured by a web-like supply chain (see Figure 2), and final products must meet specific release requirements. Because these ATs are highly perishable and unique to the specific patient, they require intricate storage, labeling, traceability, custody, packaging, and shipping requirements. The starting cellular material taken from the patient is often stored at ambient temperature, and, therefore, clinicians and couriers have only 24-48 hours to transport it from the patient to the manufacturing facility.

At the manufacturing facility, biotech companies must manage the nuances of the heterogenous cell populations of each received donor, viral transduction variability for the genetic material going into the cells, and differences in resulting cell viability. With an autologous therapy, each manufacturing run follows the same overall process; however, because the starting material differs patient to patient, the consistency and quality of each patient's result product must be carefully monitored. Once the manufacturing process is complete, the final product is evaluated per release specifications. Only then can the final product be packaged, often frozen, and shipped to the site, where it may again be stored temporarily.

The site must follow careful preparation instructions prior to administering the patient's modified cells back to him or her. Due to the personalized nature of these therapies, chain of identify ("what patient it is") and chain of custody ("who has it") are imperative to ensure integrity and accountability during the vein-to-vein process.

Being AT therapies made from a single donor, allogeneic therapies follow an important but slightly modified supply chain requirement, starting at "manufacturing" in Figure 2. The overall process, release specifications, and manufacturing considerations still apply; however, the chain of identity may be of lesser importance in the allogeneic setting, unless multiple donors and multiple cell lines are being developed.

Once the AT product is administered to the patient, another web of biospecimen samples must be collected and assayed, or processed and shipped, or stored for batching. The samples required are diverse and range from important safety labs, to immunogenicity tests, to persistence and efficacy, to unique exploratory assays. While there is not universal prescription of lab quantity or quality, each AT trial is certain to have many samples required to both protect patient safety and foster the scientific pursuit of understanding mechanisms and improving outcomes.

To ensure appropriate communication and planning, it is important that each AT trial have a dedicated individual to oversee logistics. Appropriate communication and planning are especially important for handling precious cell materials, to minimize risk at all sample handovers between patient and site and biotech or lab, and to ensure compliance and reconciliation of samples. Such measures can help to make sure a maximum of exploratory samples is obtained. Innovative technology-based solutions can also be leveraged to ensure superior compliance and tracking, as well as risk mitigation, of the logistics chain. Vendor solutions offer cold chain shipping, tracking, and custody solutions to support the specialized shipping requirements of AT studies. Finally, central repositories and/or central labs for biospecimens increase ease for and compliance of clinicians, as well as reduce shipping errors that may result in sample loss or assay integrity issues.

Such steps can ultimately improve the scientific outcomes of AT studies. Taken together, these solutions can help to manage the logistical complexity of biospecimens and materials on an AT trial.

Role of the CRO

CROs can help sponsors navigate the many operational steps involved with site selection and start-up, regulatory requirements, and product and biospecimen complexity. They can also provide data-driven guidance to enhance the probability of regulatory and clinical success.

Throughout AT trials, CROs should rely on data to assist with site identification, as well as protocol validation and optimization. In addition, they should support customers through changes in the AT regulatory landscape. For example, the forthcoming EU Clinical Trial Regulation (EU CTR 536/2014) represents the most significant change to clinical trial regulations in Europe in the 15 years since the implementation of the EU CT Directive. The EU CTR will introduce an overhaul of the procedures for clinical trial applications, amendments, and requirements for notifying authorities and ethics committees during the conduct of all interventional trials. A CRO's understanding of these regulations positions it to help customers navigate these upcoming developments.

As AT technologies evolve, we anticipate that they will become more universal and less complex. Allogeneic therapies, applicable to multiple patients, may replace autologous therapies manufactured for individuals. We anticipate that the agents in the pipeline now will result in progress and understanding in the field to decrease AT complexity. Further, a major goal is for more sites outside of high-powered medical and academic institutions to offer AT therapies, which will put them in more proximity of the patient populations they serve. Pioneering locations, such as Novartis-Penn Center for Advanced Cellular Therapeutics, a collaboration between the University of Pennsylvania's Perelman School of Medicine and Novartis, are already laying the groundwork for this. Perhaps other leading public and private institutions will follow suit, given their extensive resources. Currently, it is impractical for privately owned physician practices and dedicated sites to offer ATs, as they would need to have the technology, facilities, and infrastructure required to support specialized AT protocol requirements, support complex patient care needs, and perform bioprocessing on site. Although these are massive challenges to overcome before AT will become more widespread, the clinical trial sector is taking its first steps toward bringing these game-changing therapies to all patients who need them.

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Patient Experience Comes to Drug Development

[The transformation in patient perceptions] will only happen when the five million Americans who've already participated in clinical trials can directly share their experiences with the next five million people considering participating.

Irfan Khan
CEO, Circuit Clinical

As a clinical researcher, cardiologist, and technologist, I want to commend the groundbreaking work of Dr. Martin's MyStudies team, the FDA Catalyst team for providing the necessary data framework, and Health and Human Services (HHS) for the support of the project as covered in David Martin's article "MyStudies Platform Brings Patient Experience to Drug Development." Above all, the FDA's Patient Engagement Advisory Council—comprised of actual patients—deserves specific credit for bringing the patient voice into the design thinking for technologies in clinical research. This important and empowering project is very much a sign of the frame shift that is now upon us guiding how patients evaluate and engage clinical trials.

In this project, we can also take encouragement from the clear validation by FDA of mobile input as a reasonable and appropriate media for collection of patient feedback in clinical trials—an approach that maximizes collection opportunity and minimizes patient burden. Surely this is the path forward to making the collection ePRO and eCOA as streamlined as possible—as noted by recent advances from Medidata and others.

And in reviewing the MyStudies capabilities and functionality, additional opportunities to fully capture patient voice present themselves. As Craig Lipset, until recently Pfizer's head of clinical innovation, has observed, "There are two flavors to patient experience data—the first flavor includes FDA initiatives like MyStudies as well as patient-focused drug development (PFDD) that focus on the experience of patients with a specific medical condition or the patient experience while using a medication. These are natural and modern extensions of patient-reported outcomes (PROs)."

Lipset goes on to draw a distinction between this data set and the experience data of participation in clinical research itself. "Concurrently, research sponsors are concerned with the subjective experience of patients within clinical research studies. This flavor is an extension of sponsor initiatives themed around patient centricity and patient engagement."

Today, this second patient experience data set—which would simply ask, "What is it like to participate in a clinical trial? Would you recommend it to a friend or family?"—is the last untapped data space that could radically transform clinical trial development and execution.

And unlike our current propensity to collect and then sequester data from patients, this second patient experience data set would do its greatest good for the greatest number of people if it was patient-facing and transparent from inception.

What would be some components of such an approach to capturing this deeper, more generalizable patient experience? As noted, it would start by being patient-facing and delivering a more user intent-oriented search experience than our current best options, like the comprehensive but often overwhelming clinicaltrials.gov. In other words, it would answer the questions that patients already ask as consumers, "what should I do?" and "what do people like me think about this option?"

While we get this information shopping for shoes, cars, and even doctors, there is no equivalent for evaluating clinical research as a care option. The patient-as-consumer already has a framework in mind for online support—from Amazon to Healthgrades—and that is peer-to-peer education and support in the form of ratings and reviews. The transformation we all hope for in patient perceptions of clinical research, ranging from concerns of placebo, guinea pigs, and Tuskegee, is not going to happen as a result of greater data downloads or white papers. It will only happen when the approximately five million Americans who've already participated in clinical trials can directly share their experiences with the next five million people considering participating—in a way that is easily digested and resonates.

As we celebrate the work of the MyStudies team and address the patient experience transformation upon us, it is exciting to realize we're at the beginning of the next great opportunity to enhance how we bring new medicines to market.