NOVEMBER/DECEMBER 2017

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

Volume 26 Number 11/12 Metrics and Benchmarks Applied Clinical Trials November/December 2017

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M&A, FDA Top List of 2017 Happenings

LISA HENDERSON
Editor-in-Chief

Well, that year went surprisingly fast. A cursory glance at the industry activity that occurred in 2017 included a continuance of the WIRB-Copernicus buying spree of Medavante, ProPhase, and ThreeWire; the transfer of Parexel to private equity firm Pampoloma; Chesapeake IRB scooping up two additional IRBs, then merging with Schulman IRB to become new entity Advarra; and the big event of INC Research acquiring inVentiv Health, which is yet to be renamed. Keeping in mind the Quintiles-IMS Health merger of May 2016 resulted in QuintilesIMS and the November 2017 renaming to IQVIA.

There were other notable acquisitions—ERT's purchase of Biomedical Systems, ICON's acquisition of Mapi Group and LabCorp of Chiltern. All this is to say that the industry is shifting again. The impact of the M&As, besides rebranding and renaming, includes concern on the sponsor side. As *Applied Clinical Trials*' Editorial Advisory Board (EAB) member Townsend Barnett, Vice President and Global Head of Pre-Clinical and Clinical QA for UCB Pharma, said, "Consolidation in the CRO space is a problem for sponsors. It takes time to sort out….from SOPs to the varying vendor connections."

For 2018, the EAB members identified a number of trends outside the aforementioned business machinations. They pointed out a number of upcoming regulatory guidances scheduled for release, including ICH E6 R2; implementation of ICH E9, R1 (which hasn't been updated in 20 years and is "the bible" of statistical principles in trials, said member Stephen Senn, PhD, Head of Competence Center for Methodology and Statistics for Luxembourg Institute of Health); and also on the ICH side, ICH E19 is a new topic on when targeted collection of safety data could replace "full" collection.

Looking at the FDA, a guidance on digital health is expected this month or in Q1 2018. With the appointment of Scott Gottlieb as commissioner in May 2017, there is a more positive vibe in the pharma world that regulatory is serious about shortening trial timelines and moving them forward, either with technology acceptance or accelerated pathways or trial designs.

Late last month, we found out the EMA will be relocating to Amsterdam, which means 2018 will feature a series of building, moving, and integrating to bring the EMA to its new home by March 30, 2019.

While *Applied Clinical Trials* focuses on articles and information professionals can use in their trials today, the Board members and contributions from Ken Getz based on research from Tufts CSDD and CISCRP, highlight where industry can improve. EAB member and HL7 CTO Wayne Kubick says, "How do we implement the clinical trial of the future? There are a lot of dramatic changes that need to happen so that we can shorten timelines, take the waste out, and get things done." Last year, we did tackle that in my favorite article to date, "The Clinical Trial of Tomorrow" (http://bit.ly/2l8SIsb), which is a good roadmap to how technology will grow to improve drug development; however, holistically it will occur in fits and starts. In 2018, the hope is that industry can continue its improvements to move forward faster and more effectively.

EDITORIAL OFFICES

485 Route 1 South, Building F, Second Floor,
Iselin, NJ 08830 USA
+1 (732) 346-3080 fax: +1 (732) 647-1235,
www.appliedclinicaltrialsonline.com

EDITOR-IN-CHIEF Lisa Henderson,
lisa.henderson@ubm.com

MANAGING EDITOR Michael Christel,
michael.christel@ubm.com

COMMUNITY MANAGER Lisa Higgins,
lisa.higgins@ubm.com

ART DIRECTOR Dan Ward,
Dward@hcl.com

EUROPEAN EDITOR Philip Ward,
philipward1@btconnect.com
PO Box 114, Deeside CH5 3ZA, UK
+44 1244 538 583

WASHINGTON EDITOR Jill Wechsler
+1 (301) 656-4634 fax: +1 (301) 718-4377

SALES OFFICES

VICE PRESIDENT OF SALES/GROUP PUBLISHER
Michael Tessalone
485 Route 1 South, Building F, Second Floor,
Iselin, NJ 08830 USA
+1 (732) 346-3016. fax: +1 (732) 647-1235,
michael.tessalone@ubm.com

GROUP PUBLISHER Todd Baker
+1 (732) 346-3002,
todd.baker@ubm.com

DIRECTOR OF ADVERTISING Wayne K. Blow
UK: +44 1244 629 304 fax: +44 1925 732 798,
wayne.blow@ubm.com

NATIONAL SALES MANAGER Bill Campbell
+1 (847) 283-0129 fax: +1 (847) 282-1456,
william.campbell@ubm.com

SALES SUPPORT COORDINATOR Kristi Stevenson
+1 (732) 346-3006 fax: +1 (732) 596-0012,
kristi.stevenson@ubm.com

ACT CHESTER UK OFFICE: +44 1244 393 100

MARKETING SERVICES

AUDIENCE DEVELOPMENT MANAGER
Rochelle Ballou
(218) 740-7005, rochelle.ballou@ubm.com

C.A.S.T. DATA AND LIST INFORMATION
Melissa Stillwell
(218) 740-6431, melissa.stillwell@ubm.com

PERMISSIONS/INTERNATIONAL LICENSING
Maureen Cannon
+1 (440) 891-2742 fax: +1 (440) 891-2650, maureen.cannon@ubm.com

REPRINTS 877-652-5295 ext. 121
bkolb@wrightsmedia.com
Outside US, UK, direct dial: 281-419-5725. Ext. 121

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BACK OR CURRENT ISSUES +1 (800) 598-6008,
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PRODUCTION OFFICES

PRODUCTION MANAGER Karen Lenzen
Advanstar Communications, 131 W. 1st Street,
Duluth, MN 55802 USA
+1 (218) 740-6371 fax: +1 (408) 962-1125

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PEER REVIEWED

22 Site Perspectives on Clinical Trial Quality

Michael J. Howley, Peter Malamis, Jim Kremidas

A model to identify the services and resources sites need to conduct high-quality clinical trials.

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http://bit.ly/2n8SNTf

As *Applied Clinical Trials* continues its move to a more enhanced digital experience, be sure to visit our online digital edition of the magazine, with the same look and feel as the print! The Digital Edition Archive (link below) features a quick list of the contents for each issue.
http://bit.ly/2AB7F2p

To shed light on current industry attitudes toward collaborative R&D, SCORR Marketing, in conjunction with *Applied Clinical Trials*, conducted a survey of industry professionals. Specifically, we wanted to know to what extent these joint efforts occur, what types of groups participate in such collaborations, and why some organizations choose to collaborate and others don't. Download this free report here:
http://bit.ly/2wfONjX

GLOBAL REPORT

WHAT CAN YOU DO TO PREVENT CLINICAL TRIAL FRAUD?

Fraud prevention requires good research governance, clear peer review of activity, and mechanisms in place to investigate any allegation, and regular review of data and investigation of suspicious data, according to an experienced UK clinical researcher. Encouraging a whistleblowing culture, monitoring reports acted on by sponsors, understanding that mistakes can happen, and an open policy to "own up" are also vital.

"Fraud seriously undermines the integrity of clinical research as a whole," says Steve McSwiggan, PhD, deputy director of the Edinburgh Clinical Research Facility at National Health Service (NHS) Lothian. "The onus must be on all staff to raise any suspicions with a line manager or superior."

Clinical trial fraud is more prevalent than is thought, but is still rare, he added. The literature is littered with examples of fraud, despite most cases being dealt with in-house, and fraudsters tend to be lone workers or those who are so exalted that their work cannot be challenged.

The consequences include damage to an individual's reputation, damage to an institution's reputation, erosion of scientific trust, dangers for patients (data used may lead to unsafe medications being licensed), and denying patients access to potentially useful treatments, according to McSwiggan, who was formerly the head of commercial research services at the Tayside Medical Science Centre (TASC), University of Dundee/NHS Tayside, UK. Furthermore, the time spent validating data increases costs and reduces the time spent on building new knowledge, and fraud leads to returned fees/grants, delays in review, cost of investigations, reanalysis of data, etc.

McSwiggan believes it's important to distinguish between fraud (use of deception with the intention of obtaining personal gain, avoiding an obligation or causing loss to another party) and research misconduct (fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results). In the UK, the most relevant legislation is the Medicines for Human Use (Clinical Trials) Regulations Statutory Instrument (2004, No. 1031), and the legislation for Clinical Trial of an Investigational Medicinal Product (CTIMP), which lays down 14 principles and conditions of good clinical practice (GCP).

McSwiggan, who spent six weeks treating Ebola patients in West Africa in 2015, noted that other types of clinical trial fraud include forging (invention of false or misleading data), cooking (only analyzing data that supports a hypothesis), trimming (smoothing out data), misuse of statistics (use of improper techniques), and irresponsible authorship.

Determining a local approach that works is important, he continued in his presentation posted on the TASC website (see: http://bit.ly/2hQPQoC). For instance, NHS Tayside has a whistleblowing policy, code of corporate governance (including fraud standards), and a fraud liaison officer. The University of Dundee has a code of policy and procedures for investigating and resolving allegations of misconduct in research and a whistleblowing code.

To illustrate his key points, McSwiggan gave details of three notable case studies. Evidence suggests these are not isolated cases of misconduct, McSwiggan pointed out. The Commission on Research Integrity in Washington found in 1996 that 36% of doctoral and post-doctoral students were aware of an instance of scientific misconduct, and 15% were willing to do whatever was necessary to get a grant or publish a paper. A survey of members of International Society for Clinical Biostatistics in 2000 revealed that 51% of respondents knew of fraudulent projects.

A review of 650 FDA inspections conducted between 1998 and 2013 led to 57 official actions. There were 22 cases of falsified information, 14 cases of researchers who failed to report adverse events, 42 cases of violations of the trial's protocols, 35 cases of record-keeping errors, and 30 cases of researchers who failed to protect patient safety or to acquire informed consent.

— Philip Ward

WASHINGTON REPORT

FDA SEEKS INNOVATIVE RESEARCH STRATEGIES TO BRING NEW CURES TO PATIENTS

The main challenge in developing treatments for rare conditions is to identify, enroll, and retain sufficient numbers of patients in clinical trials to obtain meaningful information on product safety and efficacy. Since 1983, FDA has approved more than 450 orphan drugs, and new gene therapies and other scientific advances promise to yield more transformative medicines. FDA reports that some 40 companies are developing CAR-T technologies for multiple indications and that it is monitoring more than 600 active investigational new drug applications (INDs) related to gene and cellular therapies. Yet, difficulties in devising and carrying out studies on small patient populations require new approaches to clinical research and product regulation.

FDA has moved to smooth the pathway for these important products, as seen in its orphan drug modernization plan. Issued last June, it aims to facilitate timely review of a soaring number of orphan drug designation requests, reported FDA Commissioner Scott Gottlieb at the annual meeting of the National Organization for Rare Disorders (NORD) in October. FDA officials described strategies for more efficient product testing, such as cross-over and randomized withdrawal studies suited to very small studies, and emphasized the importance of sponsors seeking early discussion of outcomes measures and target product profiles. And collaborative research platforms that share resources and data can help speed the path of effective treatments to patients, noted Petra Kaufmann of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH).

Gottlieb and others also emphasized the importance of developing natural history studies on how critical diseases arise and progress to help identify symptoms to treat and patients to test to obtain meaningful data on important endpoints. FDA recently awarded its first research grants to fund natural history studies, and NCATS is supporting research projects in this area. FDA's orphan products grants program funded the new grants, along with 15 awards supporting early phase studies on rare diseases.

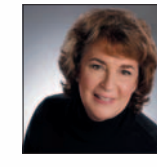
Additional assistance and accelerated reviews are available for important cellular and gene therapies under FDA's new program for developing regenerative medicine advanced therapies (RMATs), which is overseen by the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research (CBER). FDA recently unveiled a regenerative medicine regulatory framework, as specified by the 21st Century Cures Act.

Advocates important

FDA and sponsors acknowledge the increasingly important role of patient advocates in encouraging trial enrollment and design of studies that consider critical symptoms and hard-to-manage side effects. FDA has held dozens of patient-focused drug development meetings over the past five years to gain the views of patients and families on treating certain conditions and now is encouraging independent patient groups to organize their own R&D programs.

This approach is being formalized for medical devices, as seen at the first meeting of FDA's Patient Engagement Advisory Committee (PEAC), which discussed effective methods for recruiting diverse patient populations and how requirements for informed consent, randomization, and study duration affect trial enrollment and retention. Established by the Center for Devices and Radiological Health (CDRH), the PEAC seeks to bring patient perspectives into the process of designing trials that incorporate real-world evidence and patient-reported outcomes. Patient representatives on the panel advised sponsors on outreach strategies for recruitment and on how reimbursement, transportation, and other support can reduce the burden of participation in trials.

Mobile health technologies may further encourage patient participation and retention in clinical trials. Wearables that measure temperature or detect falls can facilitate studies run at home, and monitors for blood pressure and levels of cholesterol or vitamin deficiencies in the blood may lower the bar for patient enrollment. Commissioner Gottlieb unveiled an R&D plan last June to encourage new mobile devices and software development, and last month FDA approved the first digital pill, a version of antipsychotic drug Abilify that contains a tiny chip able to send a signal to an adhesive patch that informs a smart phone when the pill is ingested.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

11/9/17: S5(R3) Detection of Toxicity to Reproduction

11/8/17: Use of a Drug Master File for Shared System REMS Submissions (draft)

11/6/17: Recurrent Herpes Labialis: Developing Drugs for Treatment and Prevention

11/6/17: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industryt (draft)

11/2/17: Controlled Correspondence Related to Generic Drug Development (draft)

The following committee meetings were scheduled for November and December:

- The Bone, Reproductive and Urologic Drugs Advisory Committee ***Dec. 7***
- Blood Products Advisory Committee ***Dec. 1***
- The Antimicrobial Drugs Advisory Committee ***Nov. 16***

EU REPORT

THE 'WHAT IFs' OF EMA RELOCATION DECISION

All attention is now focused on Amsterdam and how the transition will work for the European Medicines Agency (EMA) as it relocates there over the next 16 months. But because the final decision emerged from a mere toss of a coin, after so much energetic lobbying and intense planning, it is not out of place to reflect for a moment on the what-might-have-been if the decision had gone a different way.

The rich variety of glossy brochures and videos and picture-laden websites that the candidates produced to back their bids are now nothing more than trash scattered along the European wayside. But they offer a glimpse of other futures, other lives, other possibilities—the what-might-have been for tens of thousands of Europeans linked to the world of pharmaceuticals. The choice of a new site for the agency affected not only the hundreds of staff of the agency and their families, but also the academics, researchers, officials, industry executives, and representatives of patients and health professionals representatives who are professionally obliged to spend much of their lives in and around and on their way to and from the agency.

Of course, much would have been the same wherever the choice had fallen: an office building, meeting rooms and hotels, an airport, the minimum services of a big city—the almost universal claims to be "the best country to host the EMA" effectively cancelled each other out. So, too, did the standard promises that EMA officials and families and visitors could enjoy an "international spirit," a "thriving artistic and cultural environment," or "a unique food scene." But on many of the formal criteria, the differences perceptible through the optimistic tone of the respective public relations exercises were often stark.

Accessibility—a key consideration for the 36,000 journeys a year made by experts attending meetings at the agency—varied widely. The conclusions were all too obvious that could be drawn from, say, Barcelona's connectivity ("the 7th busiest airport on the continent" with "direct flights throughout Europe") or Bonn's "three international airports in close proximity and links to major European roads and rail routes," compared with Zagreb's offer (of "regular bus lines connecting it to all parts of Croatia but also to many European cities and towns"). Lille based its appeal on being "the nearest European city to London" and "less than 35 minutes from Brussels." Curiously, Milan tried to bolster its appeal by providing travel details that showed that Vienna could be reached in 13 hours!

The cost of living and of operating the agency featured frequently in the bids. Bucharest described itself as "cost-effective." But EMA families could have enjoyed even greater spending power in Zagreb, which boasted of being "the cheapest capital in the EU." Bratislava emphasized its "lower operating costs," and Brussels tried to score points on the economic front, too, arguing that "the proximity of EU institutions reduces travel expenses."

The facilities offered ranged from the sublime to the basic. "Hospitality" was brandished as "part of the Athens daily routine," and its proposed office location offered "shopping malls, amusement parks, and multiplex cinema theaters," as well as "close proximity to the Piraeus port and the Athens seafront riviera." Bucharest's more austere bid noted "on-site amenities such as bank branches, a pharmacy, a supermarket."

Other distinctions emerged in quality-of-life amenities, such as the proximity of "Italian art cities, the Alps and the Mediterranean coast" that Milan promised, or Bucharest offering "the Carpathian Mountains, the unique Danube Delta, and the impressive Black Sea" just two hours away by car.

Geography and climate also featured prominently in bids: Malta "at the crossroads of the Mediterranean," with "300 days of sunshine a year" vied with the "excellent climate" of Barcelona. Porto substantiated its bid with the observation that "being the westernmost country in Europe, with the same time zone as the UK, Portugal has a privileged geographic location to act as an intercontinental platform, bridging the gap between Europe, America, and Africa." And both Zagreb and Brussels claimed to be at "the heart of Europe."

Some of the claims were highly individualistic—if sometimes of questionable relevance. Stockholm threw in the fact that the Nobel Prize is based in Sweden. Malta flaunted the contribution made to quality, safety and efficacy of medicines by "the Holy Infirmary of the Knights Hospitaller of Saint John over four hundred years ago."

As it is, Amsterdam will be the host city—and the resentment that flared up among many losing candidates may in time be tempered by the reflection of the agency's boss, Guido Rasi, speaking on the day after the decision was made. A coin-toss between a good candidate and a bad one would have been undesirable as a way of making the decision, he conceded. But the coin-toss between candidates of broadly similar merit was not an unreasonable approach, he said. After all, for him, and for pharma executives everywhere, what matters most is not the city, but how far the agency's operations keep running smoothly.

— Peter O'Donnell

EMA NOTES

GMPs FOR ADVANCED THERAPIES: The European Commission has published a set of guidelines on good manufacturing practice (GMP) specific to advanced therapy medicinal products (ATMPs)—those based on genes or cells. The guidelines address the novel and complex manufacturing scenarios used for these products. View here: bit.ly/2zscxCK

EUDRAVIGILANCE UPGRADE: The EMA launched a new and improved version of EudraVigilance, the information system of suspected adverse reactions to drugs that are being studied in clinical trials in the European Economic Area (EEA). The new system makes it easier to report suspected adverse reactions. View here: bit.ly/2t4iqqS

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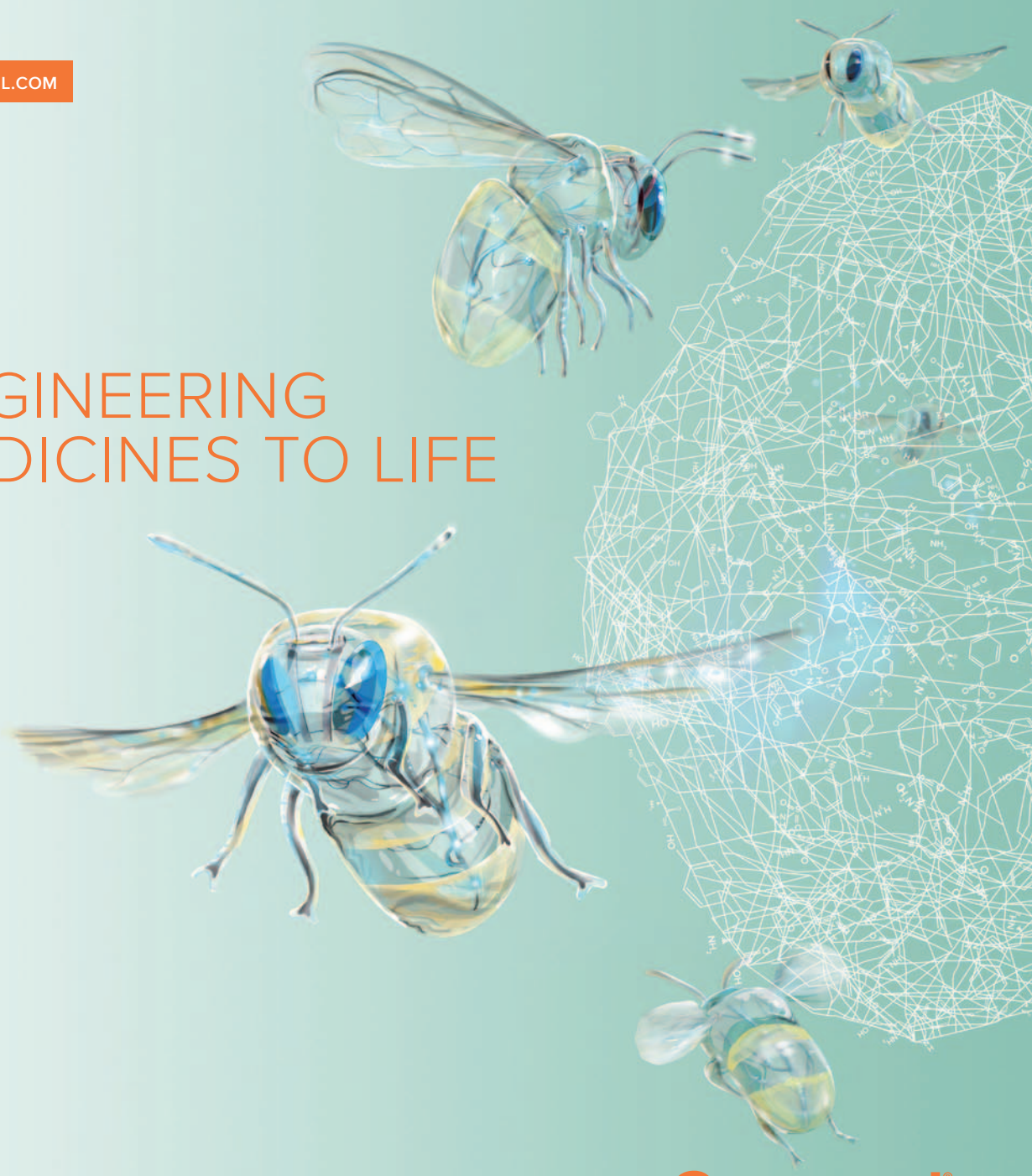

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CLINICAL TRIAL INSIGHTS

ANTICIPATING THE GROUNDSWELL OF RWD AND RWE USAGE

Study examines the growing integration of real-world data and evidence and the remaining roadblocks to adoption

Ken Getz

This past year has seen fervent attention on the use of real-world data (RWD) and real-world evidence (RWE) to support drug development, patient safety, and commercialization activity. The number of internal discussions, conferences, and publications focusing on RWD/RWE have increased dramatically, largely in response to the 21st Century Cures Act of 2016 requiring the FDA to implement a framework for RWE's role in drug development within two years.

The Tufts Center for the Study of Drug Development (Tufts CSDD) conducted a recent study to gather baseline data on current and planned uses of RWD and RWE, operational approaches that support the use of this data, and return-on-investment metrics.

Thirteen pharmaceutical, biotechnology, and contract research organizations (CROs) participated in a working group study to identify key areas of inquiry and to develop an in-depth survey instrument. And 30 distinct companies provided complete responses to the online survey.

Among the key insights from this study:

- The majority of drug development organizations report that commercial functions are currently the primary centers for RWD/RWE; only 40% report having primary centers within R&D functions.
- RWE functions plan to increase headcount substantially within the next three years as organizations anticipate that RWD/RWE will support a wide and growing range of decisions, from product positioning and market access to patient recruitment and risk management analysis.
- Organizations expect strong growth within three years in the use of social media, mobile health, and wearable device data sources to support new drug registrations. More modest growth is expected in the use of electronic health and medical record data and electronic medical imaging data during this time frame.
- The use and integration of RWD and RWE poses a number of challenges associated with data availability, reliability, quality of data sources, the cost of data acquisition and integration, and acceptance by key stakeholders (i.e., regulatory agencies and payers). Until these challenges are addressed, the utility of RWD and RWE is limited.

Underlying experience and operating models

Based on sponsor and CRO reports, RWD and RWE are used widely to support R&D, health economics, and outcomes research. The majority of responding companies have functions that have worked with real-world data and evidence, on average, for seven years. Nearly two-thirds (63%) of organizations report that their primary centers managing RWE reside within commercial functions, including epidemiology health economics and outcomes research and medical affairs. Slightly less than four-out-of-10 companies report that their primary RWE hub operates within the R&D division.

Most companies report that RWD and RWE use is managed centrally, but variation in operating approaches is observed between large versus small and mid-sized companies. Nearly 70% of large companies (annual sales greater than $11 billion and R&D spend greater than $2 billion) and 58% of small and mid-sized companies report that their RWE function is centralized and globally supporting other functional areas.

Across all companies, average fixed headcount dedicated to RWE departments are nearly double the average variable contract services headcount (mean of 19.1 fixed fulltime equivalents vs. 10.7 contract FTEs). Large companies have an average of 88.8 FTEs compared with 12.6 FTEs at small and mid-sized companies.

Responding companies expect a 25% increase, on average, in fixed and contract FTEs by 2020. Large companies project a 34.5% increase in staff by 2020. Small and mid-sized companies project a 16.8% increase in total FTEs dedicated to managing RWD and RWE use in that time frame.

Diverse data types

Pharmaceutical and biotechnology companies and CROs responding to the survey report using a variety of data elements to support a new drug application (NDA), including: claims data (used by 95% of survey respondents), electronic health record clinical data (71%), prescription data (67%), patient-reported outcomes data (48%), and demographic data (48%). Approximately four-out-of-10 (38%) and three-out-of-10 (29%) companies report using biomarker and genomics data and protocol feasibility data, respectively.

RWD and RWE are becoming essential to evaluating clinical and financial value. Respondent companies indicate that the foremost use of RWE is to evaluate and improve the economic value of their drug products (75%) and to strengthen product positioning in the marketplace (75%).

Companies also report using RWD and RWE to support critical decision-making associated with product effectiveness (63%), patient recruitment (50%), and improved completion of post-marketing requirements (46%). Less than one-third of companies report using RWD and RWE at this time to support portfolio decisions (34%), investigative site identification (29%), signal detection for risk management (29%), reduction in overall R&D development resource and financial investment (25%), and to capture product quality measures (21%).

Companies project the highest relative growth in the use of social media data (up 42%) by 2020, as more reliable and efficient means of gathering these data grow. Use of data from wearable and mobile devices is also expected to see higher relative levels of growth in usage by 2020, as more of these data sources are validated. Use of claims and prescription data—two relatively established and mature data types—is expected to decline during the next three years.

Primary challenges

Six-out-of-10 companies report that the availability of RWD and RWE data poses the greatest challenge at this time. Lack of external stakeholder trust in RWE (35%) and the cost of acquiring data (25%) were the second- and third-most cited challenges.

CLINICAL TRIAL INSIGHTS

Other challenges identified include determining causation (20%), and quality and reliability of claims and electronic health record data (15%).

One-in-five organizations (20%) cite the cost and effort of data integration. This finding echoes that observed in another recent Tufts CSDD study looking at the high volume and diversity of clinical research data now being handled by the data management function. In this study, of nearly 257 unique sponsors and CROs, the majority reported that the primary electronic data capture (EDC) system is managing electronic case report form data and lab data. But all other data types, including biomarker, electronic clinical outcomes data, patient-reported outcomes data, pharmacokinetic and pharmacodynamic data, and mobile health data represent a very small proportion of the total data captured in the primary EDC. This study also found that the cycle time from last patient last visit to data lock (now averaging 36.3 days) is longer than it was 10 years ago in part due to integration and data loading challenges.

Closing thoughts

A high proportion of companies cite the lack of trust among regulatory agencies, health authorities, and payers as a major challenge to adoption. Moving forward, steps to improve receptivity and acceptance among these stakeholders will go far in helping to realize the tremendous potential of RWD and RWE.

Also, growing demand for RWD and RWE will not be fully realized given the challenges associated with the high cost and effort required at this time to collect, integrate, and use this data. Most organizations concede that they lack the in-house expertise to manage the volume and diversity of data that organizations are eyeing to support robust inferential and predictive analyses. These conditions favor the emergence of new technologies that integrate disparate data sources such as HL7's FHIR® and the semantic web. They also favor consultants and contract service providers well positioned to assist sponsors and CROs in achieving the dynamic level of data integration required.

— Ken Getz, MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCRP, both based in Boston, MA. email: kenneth.getz@tufts.edu

Q&A

ADDRESSING ADMINISTRATIVE AND ADHERENCE BURDENS IN CLINICAL TRIALS

In early October, Janssen Research & Development, LLC announced the Integrated Smart Trial & Engagement Platform (iSTEP), a first-of-its-kind information technology toolset developed to automate investigational product supply and data management in clinical trials (view: http://bit.ly/2zUw5Uo). Developed by Janssen, in collaboration with Tata Consultancy Services (TCS), the tool is available for industry-use and is designed to replace the paper-based processes of managing clinical supplies and tracking patient health data with a cohesive suite of digital technologies.

In the Q&A ahead, Andreas Koester, MD, PhD, Vice President, R&D Operations Innovation at Janssen, discusses iSTEP, the platform's history, and its future potential.

Q: When did you start developing the iSTEP Platform with TCS and what precipitated that idea?

KOESTER: Janssen began exploring a digital platform for medication management and patient engagement more than five years ago. At that time, we realized while there were many standalone solutions available in the marketplace—smart bottles, smart blisters, medication scanners—we were missing a comprehensive, mobile toolkit with the ability to address two key pain points in clinical trials: investigator administrative burden and patient information/adherence.

We started interactions with TCS on iSTEP toward the end of 2014. They are a leading global IT services, consulting, and business solutions organization with a very strong IT business. We had confidence in their technology prowess and experience in clinical trial IT to collaborate with us and build such a platform.

Q: This is not related to TransCelerate, but you encourage other pharma to adopt for a consistent approach across the industry. How are you doing that?

KOESTER: The open innovation philosophy at Janssen led us in collaboration with TCS to develop iSTEP in a way that allows the technology to be adopted by other pharmaceutical companies. We believe that a consistent approach across the industry can accelerate processes to bring medicines to patients faster, and at a lower expense.

We've proactively engaged a number of companies and informed them about the platform in December 2016 and held a readiness meeting in June 2017. At the meeting in June, we presented the platform to 26 R&D leaders of eight global pharmaceutical companies, and many expressed interest.

Q: Is this a cloud-based approach?

KOESTER: Yes, similar to many other eTechnologies services like electronic data capture (EDC) systems, etc.

Q: What were the challenges and benefits you learned in the pilot?

KOESTER: A core challenge was that this was a huge development with many different system and device integrations, which is always a challenge and a big reason why so little actually had been done across the industry to that point.

We learned that site personnel, sponsor personnel, and participants were overall very positive about their experience with the smartphone and smart blister. We received enthusiastic feedback on the platform's usability and remote-monitoring capabilities. The pilot also verified that all of the iSTEP components worked in an integrated manner.

Q: What feedback have you had from the regulatory authorities as you attempt the tool's use in a clinical trial?

KOESTER: Feedback to date from regulatory authorities has been very positive. We do expect to have all necessary approvals to begin using iSTEP in a study by the end of the year.

Q: Can you share the size/phase and TA of the intended trial?

KOESTER: We plan to implement iSTEP in a Phase II trial by year's end, and don't have additional information that we can share at this time.

Andreas Koester, Janssen's Vice President of R&D Operations Innovation

Q: Are there any plans to expand iSTEP into other clinical trial operation aspects?

KOESTER: Yes, we are always exploring new opportunities to expand iSTEP and reduce the complexities of clinical trials with the benefit of patients and investigators in mind. To this end, we see the iSTEP platform as the backbone for future utilities to be added, e.g., eICF, ePRO, sensor data feeds. We are on an exciting journey.

— Staff Report

NEWS NOTES

REPORT HIGHLIGHTS LACK OF PREPAREDNESS FOR AN ALZHEIMER'S TREATMENT

The RAND Corporation issued a recent report indicating that the US healthcare system is not prepared to handle the expected large number of patients if additional Alzheimer's therapies become available in the next several years. According to the report, a treatment could become available by 2020 but millions of people would have to wait an average of 18 months to receive a drug, largely because of a shortage of neurologists qualified to make a diagnosis. RAND estimates that as many as 2.1 million patients would develop Alzheimer's between 2020 and 2040 while on waiting lists for treatment. Read the report here: http://bit.ly/2Auclqf.

ERT acquires iCardiac Technologies

ERT, a global data and technology company, has acquired iCardiac Technologies, a provider of centralized cardiac safety and respiratory solutions that accelerate clinical research. Financial terms of the transaction were not disclosed. The deal enables ERT to expand its portfolio of cardiac safety solutions, specifically through the addition of iCardiac's algorithm-driven technology, which supports efficient and regulatory-compliant methods of conducting QT assessments in early phase clinical trials.

Science Exchange, Alector partner

Science Exchange, an enterprise platform and aggregator for outsourced R&D, has struck a strategic partnership with Alector, a biotech company pioneering the discovery and development of immuno-neurology therapies for neurodegenerative disorders. Alector's scientists will be given access to the Science Exchange-powered R&D marketplace, which enables the ordering of more than 6,000 scientific services from 2,500 contract research organizations (CROs), academic labs, and government facilities.

Mega IRB merger

Two prominent research industry institutional review boards (IRBs), Chesapeake IRB and Schulman IRB, have combined to form Advarra, creating a premier provider of IRB, institutional biosafety committee (IBC) and research compliance services in North America. The new organization will leverage mutual strengths in technology, regulatory expertise, and customer service.

New drug class pursuits get boost

Biotech Arvinas LLC has expanded its license agreement with Genentech for the development of drugs using Arvinas' PROTAC technology, which induces protein degradation and may potentially target "undruggable" as well as "druggable" elements of the proteome.

— Staff and wire reports

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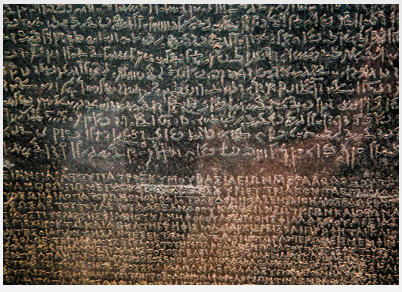
CLINICAL DATA STANDARDIZATION

CDISC GLOSSARY OF CLINICAL RESEARCH TERMINOLOGY

A Rosetta Stone for clinical research

The world of clinical research includes participants from many sectors: the pharmaceutical industry, government agencies, academia, healthcare providers, subjects, patients, technology providers, and many others. While there may be the perception that a *lingua franca* has evolved through common usage, this is not the case. We may find ourselves using common terminology, yet the strict definitions and interpretations of these words often differ markedly. This is not due solely to differences in native language or culture, but to the multiple "authoritative sources" of clinical research applicable definitions, including FDA, EMA, ICH, WHO, International Organization for Standardization (ISO), and specialty groups that code and use terminology for healthcare, payers, hospitals, and other stakeholders. While, in principle, the Glossary addresses global use, the primary sources of definitions are based on those derived from U.S. and European standards organizations and regulatory authorities.

Add to this scenario the need to ensure that information provided is both human- and machine-readable—a concept called "interoperability." This really was the genesis point for CDISC—evolving, of necessity, as a standards organization at the beginning of the age of electronic data collection, analysis, and submission to regulatory authorities in support of new drug applications for marketing approval.



The long-standing Mission Statement for CDISC's Glossary Group—the longest-serving working group under the CDISC umbrella (convening for the first time in 2002)—echoes these origins:

> *CDISC Glossary seeks to harmonize definitions (including acronyms, abbreviations, and initials) used in the various standards initiatives undertaken by CDISC in clinical research. Glossary also serves the community of clinical researchers by selecting and defining terms pertaining to clinical research, particularly eClinical investigations, sponsored by the pharmaceutical industry or a federal agency.*

Recently, it has become apparent that the clarity and comprehension provided by the Glossary supports colocation and translation of the concepts in the many countries where research is done, and the resulting products are used.

Thus, the Glossary is intended to serve both novice and experienced users as an authoritative advisory resource in the context of clinical research and development. To accomplish this, it was necessary to identify recognized sources of definitions, clarify differing contextual interpretations, and, as much as possible, harmonize across a global landscape of word usage. It should be emphasized that the Glossary Group is not a standards development body but, rather, one that has developed an aid to better understanding the terminology.

Occasionally, the members of the group made modifications to definitions in order to better represent the most common use or, when no authoritative source was identified, defined the term, based on their extensive collective experience in the conduct of clinical studies; collection, analysis, and interpretation of data derived from those studies; and long-standing roles in the development of CDISC models for protocols, data standards, and collaboration with regulatory authorities worldwide.

The CDISC Glossary Version 11.0 adds to the four groups of new terms included in last year's update: Milestones, eSource, Transparency, and Clinical Trial & Clinical Study. This year's Glossary expands the Outcomes Assessment (and eCOA) and endpoints; and includes some new terms from ISO for the identification of medicinal products (IDMP), the ICH E6 update, and elements from the Common Protocol. The NIH-FDA BEST (Biomarkers, Endpoints, and other Tools) Resource, which contains FDA-NIH harmonized terms used in translational science, is included the Glossary's Reference Citations section. Specific terms are included in this year's update.

An additional technical update made this year is that the CDISC glossary content will be integrated into the NCI Thesaurus (NCIt; ncit.nci.nih.gov), an open source, publicly available biomedical coding terminology developed by the U.S. National Cancer Institute's Enterprise vocabulary services (NCI-EVS).

Examples of operational issues addressed in the course of the Glossary development include:

More than Words

Preferred Term	Synonym(s)	CDISC Definition	Source
clinical outcome assessment (COA)		Clinical outcome assessment. Any assessment that may be influenced by human choices, judgment, or motivation and may support or refute treatment benefit. NOTE: Unlike biomarkers that rely completely on an automated process or algorithm, COAs reflects interpretation of reporting from a patient, a clinician, or an observer. There are four types of COAs. See also patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO).	[After Clinical Outcome Assessment (COA) Glossary of Terms FDA FDA eCOA Glossary]
feels		**feels.** A patient's physical sensation (e.g., symptoms) or perceived mental state. A patient may feel pain, feel feverish, or perceive a severely low mood (as with depression).	[Clinical Outcome Assessment (COA) Glossary of Terms FDA FDA eCOA Glossary]
functions	functioning	**functions.** The manner in which a patient can perform successfully tasks and roles required for everyday living. A patient's ability to perform specified activities that are a meaningful (to the patient), part of typical (e.g., daily) life.	[Clinical Outcome Assessment (COA) Glossary of Terms FDA FDA eCOA Glossary]

Table 1. Example of Excel table providing links to related information.

CLINICAL DATA STANDARDIZATION

• **Providing useful resources beyond the term definition.** Although the focus of the Glossary is to define commonly-used terms, the group determined that there would be great added value in providing links to associated information. These allow the user to further explore context and nuance that cannot be accommodated in the Glossary itself. Table 1 on facing page shows an example of the Excel table.

• **Multiple interpretations.** On occasion, there were multiple legitimate definitions that needed to be considered. These definitions usually differed due to associated context. Thus, in order to recognize this, we provided these definitions with explanatory notes that conveyed the rationale and appropriate use. Older versions of the Glossary were organized like a dictionary of terms, without supporting the sorting and searching utilities that enhance review of a tabular format. This year, for the first time, the Glossary and its many formats can be filtered and the terms are unique (see Table 2). Each unique term has a single definition and synonyms, or similar terms, are noted.

• **Enhanced functionality.** Adding this new and long-awaited feature to enable easier searching and readability, the Glossary has been updated to a PDF-based tabular format with searchable functionality. Terms can be sorted and filtered. Thus, it is truly sortable, linkable, and serviceable as a "go-to" reference tool. This version is remarkable in that it will be available in six different formats and more suited for digital download and use. These are Excel, Windows text file (.txt), odm.xml, pdf, html, and OWL/RDF formats.

• **Term selection and organization.** Terms were carefully selected to ensure that they were germane to clinical R&D. We provide definitions that are, hopefully, sufficient to gain a basic understanding of the term and context. As noted earlier, the links to the source(s) are provided should the user wish to go into more depth. Terms are co-located and electronic searching is augmented by "child-parent" term organization.

• **Historical ambiguity.** Some terms carry with them long-standing confusion among users. We have addressed, as much as possible, ambiguity in existing reference source definitions and provided clarification. Some examples are the often synonymous but confusing use of "dose" and "dosage", as well as "study" and "trial." An example of the Excel table is shown in Table 3.

Better Sort and Search

CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	Changes
~~application~~		~~**application.** 1. Computer application: software designed to fill specific needs of a user; for example, software for navigation, project management, or process control. 2. Regulatory application: application made to a health authority to investigate, market, or license a new product or indication. Synonyms: 1. computer application, application software.~~	Retire concept and split into Computer Application and Regulatory Application.

Table 2. Example of Excel table showing terms now filtered to a single definition, with synonyms, or similar terms, noted.

Clearer Meanings

CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	Changes
investigational product		**investigational product.** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. NOTE: CDISC includes test articles in its definition of investigational products. Compare with Investigational Medicinal Product (IMP) from EU-CTR (EU) No 536/2014. [ICH]	Update definition.

Table 3. Example of Excel table addressing ambiguity in existing reference source definitions.

• **Acronyms, abbreviations, and initials.** Links will also be provided in the Glossary to access acronyms, abbreviations, and initials. The *Acronyms, Abbreviations and Initials* list was not comprehensively updated during the Glossary update cycle for Version 11.0.

The future: Watch this space

Next year, the CDISC Glossary Group will continue to address concepts introduced and presented in new guidelines. As technology and globalization continue to evolve, we will be taking on the impact of guidances like the EU Clinical Trials Regulation (CTR) that goes into effect when the European database is operational. We will also continue to address concepts around transparency and disclosure as the pharmaceutical industry and regulators wrestle with the pragmatic logistics of providing timely and useful information to the research community, while protecting patient privacy.

We test links to sources for individual terms and, while not all terms are updated each year, we will reassess terms periodically to ensure currency. Although the Glossary is now available in six formats, we will be exploring how to optimize it for use on handheld devices.

WHERE TO FIND THE CDISC GLOSSARY

• **CDISC website:** https://www.cdisc.org/standards/semantics/glossary

• **NIH EVS website:** https://www.cancer.gov/research/resources/terminology/cdisc

— Authors of this report and Glossary Team members: ***Art Gertel****, Principal, MedSciCom, LLC;* ***Helle Gawrylewski*** *(Team Chair), MA, Sr. Director, Janssen R&D Companies of J&J;* ***Steve Raymond****, PhD, Chief Scientist, Scientific Affairs, ERT;* ***Erin Muhlbradt****, PhD, Clinical/Biomedical Information Specialist, Enterprise Vocabulary Services, National Cancer Institute*

Contributors/Glossary Team members: ***Denise Adelman****, Global Process, Senior Analyst, J&J;* ***Guido Claes****, Director, Master Data Standards, Global Clinical Development Operations, Janssen R&D Companies;* ***Melissa Cook****, Senior Management Consultant, MC Consulting;* ***Jon Hilton****, Global Data Standards Manager, F. Hoffmann-La Roche Ltd*

We would also like to acknowledge the assistance of CDISC staff and SIRO Clinpharm.

Salary and Satisfaction

Weighing overall workplace trends in industry with new survey results

Lisa Henderson

To close out 2017, we wanted to gather the clinical trials professional's view of salary and satisfaction in their current role. *Applied Clinical Trials* and our survey partner, SCORR Marketing, fielded the survey from the end of September to the end of October, garnering 226 respondents, one of our highest to date. The majority of the respondents work for a biopharma company (25%); in clinical operations (35%), and in a managerial role (28%).

Of course, other factors come into play for actual pay, including the role, function, geographic location, education level, and others, and some of these demographics are included in the full report.

For this article, we look at overall trends in salary and satisfaction, compared with our results, as well as other organizations that monitor professional information for the life sciences industry. **Please download our free report at http://bit.ly/2hVr1nE**

SALARY SURVEY

Hiring trends

According to a Q2 2017 Global Life Sciences Hiring report, nearly every geography in every functional need across life sciences decreased, except R&D. ZRG Partners, LLC, a global talent management firm within the life sciences, pharmaceutical, and medical markets, noted that R&D accounted for an 11% gain over the same period in 2016. The outsourcing/services sector comprised 43% of the R&D jobs.

A review of the major geographies also showed the most significant decline was in the EMEA, with a 20% drop from this time last year. ZRG attributed it to reduced activity at key industry leaders. This activity also contributed to a 14% year-over-year decline in North America. ZRG European President and Global Practice Head of Life Sciences, Adam El Din, said in a release, "The pharmaceutical and healthcare sectors in the Middle East and North Africa (MENA) region will be affected by several factors during the entirety of 2017, including a slowdown in public sector growth as a result of low oil prices, regional challenges on the back of heightened pressure on drug prices and economic instability."

YEARS IN CURRENT ROLE

3 to 5 years	19%
6 to 10 years	18%
1 to 2 years	16.5%
11 to 15 years	14%
More than 20 years	13%
Less than 1 year	12.5%
16 to 20 years	7%

Source: *Applied Clinical Trials*/SCORR Marketing survey, October 2017

The response breakdown to survey question: how many years have you worked for your current employer?

David Fortier, Managing Director – Global Life Sciences, at ZRG, added, "While results over the past year show a trend of reduced hiring activity, it is important to note that hiring overall remains robust, with this quarter posting the fourth-highest quarterly index score in the past eight years."

Overall satisfaction

As mentioned, the majority of our survey respondents were from clinical operations, followed by R&D (15.5%) and project management at 14%. The "other" category comprised another 15% and included nursing, medical affairs, and investigators. However, by far the most in that category was clinical research coordinators.

While this begs us to delve deeper into the specific job titles for our next survey, we did ask respondents about

overall job satisfaction in the following areas: salary/compensation, training/continuing education, career development, job responsibilities, and current position. On a scale of 1-5, 1 being low and 5 high, satisfaction with job responsibilities came in at an average of 3.5 and salary at 3.27. The lowest average was career development opportunities at 2.67. The good news is, more than half of the respondents (56%) are not looking for a new job. Those that are cite a variety of reasons, many around the lack of career development opportunities, which include insufficient career development options, professional advancement, and inadequate training/continuing education opportunities.

For the majority, inadequate resources was chosen as the most challenging aspect of their job in the past year. However, even for those respondents, the majority (52%) are not actively seeking a new position.

Turnover

Historically, turnover is viewed negatively both internally and externally. It can signify internal managerial problems; internal corporate problems; moves for higher compensation among those highly-skilled, high-demand positions; and more. In clinical trials, certain roles impact the business of a trial more acutely, and usually they are in the roles that touch the site or the pharma sponsor on a regular basis. According to Judy Canavan, managing partner, HR+Survey Solutions, turnover is extremely costly to CROs. "Turnover is a significant business issue; high turnover can undermine the relationship with a sponsor or lose a bid for new work," she said in a release last year. Those reasons include the following:

- Create a loss of continuity that can lead to delayed timelines.
- Increased costs as a result of lower productivity, increased workload on colleagues, onboarding costs, loss of knowledge, recruitment costs.
- Impact business development as sponsors scrutinize turnover in their vetting process.

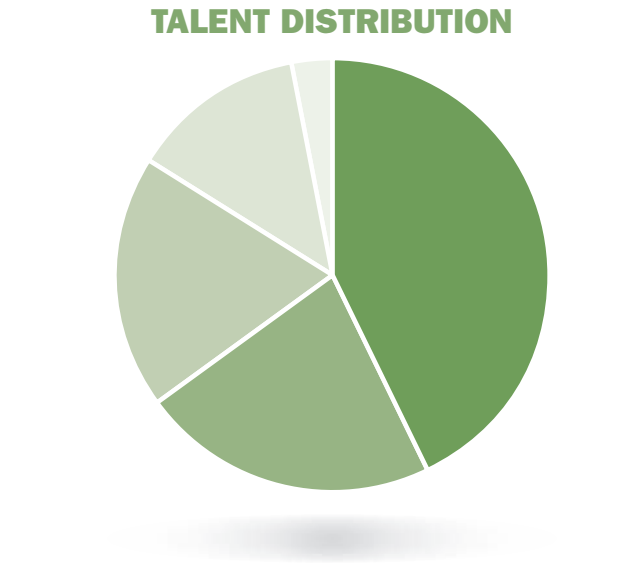
HR+Survey Solutions' 2017 CRO Industry Global Compensation and Turnover Survey found that overall average turnover at CROs in the U.S. increased slightly to 21% in 2016 from 20.1% in 2015. That is for all positions at CROs. The top 10 countries with the highest turnover for 2016 were Taiwan, China, Hong Kong, Thailand, Malaysia, Switzerland, Sweden, Mexico, Singapore, and Turkey, with turnover ranges from 42% to 25%.

According to HR+Survey Solutions, 47% all trials are non-U.S. only, 36% are U.S. only, and 5% are both U.S. and non-U.S. With the highest number of trials being conducted outside the U.S., these continual increases in turnover rates become more important. With the year-over-year industry growth predicted to continue in the CRO industry, attracting and retaining talent is a key factor to a successful business model. According to the report, U.S. unemployment has continued to decline since it peaked in 2009, and currently is below 5%. This means that CROs have an uphill battle identifying new talent sources. Canavan suggests that CROs need to create customized approaches to retain the right talent for their company to minimize costly turnover scenarios.

Globally speaking

Our survey included 67 respondents from Europe. Their results compared pretty equally with those in the U.S., with the following outliers:

- 30% worked in biopharma and 24% in CROs.



The most active life sciences outsourcing/services jobs by function.

- Slightly lower averages on overall job satisfaction rates.
- Challenges in the past year, inadequate resources, and changing role or lack of defined role were rated equally at 19%.

In a recent discussion around industry trends with the *Applied Clinical Trials* Editorial Advisory Board, it was noted that the increased use of CROs for clinical development activities by pharma creates its own resource issues. Specifically, the need for increased oversight by pharma of its outsourced providers. Additionally, if a company outsources for a specific expertise area, it does not internally possess it; that in and of itself creates a problem for oversight. You can't measure what you don't understand.

These and other topics related to professional sourcing in clinical development will be featured in our March issue. "Talent: Where is your talent going and where will you find more?" will look at current recruitment trends, pharma vs. CRO balance, new industry titles or roles and responsibilities, and more. We will be accepting articles for peer-review for this issue. Please submit your articles regarding training and development initiatives; human resource directions; or other related articles to actspecialprojects@ubm.com and/or lisa.henderson@ubm.com.

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Site Perspectives on Clinical Trial Quality

Michael J. Howley, Peter Malamis, Jim Kremidas

A model to identify the services and resources sites need to conduct high-quality clinical trials.

PEER REVIEW

Site perspectives of clinical trial quality are rarely heard, even though they are the foundation of the clinical research enterprise. But sites are not alone in conducting trials. They depend on sponsors and contract research organizations (CROs) to provide services and resources that allow them to execute a trial. The critical question from the site's perspective then becomes: What are the essential resources and services that sites need from sponsors and CROs in order to conduct high-quality trials? The purpose of this paper is to identify such services and resources that are associated with high-quality clinical trials.

This study focuses on three research questions (RQs):

- **RQ1:** What are the coproduction activities that sponsors and CROs provide to sites that lead to high-quality trials?
- **RQ2:** How do sites evaluate sponsors and CROs on these key drivers of quality?
- **RQ3:** How do each of these coproduction activities drive clinical trial quality?

To answer these questions, we conducted focus groups to identify all the activities that are important to sites (RQ1). To evaluate RQ2 and RQ3, we loaded all of these activities, as well as a measure of clinical trial quality, into an online survey. We then solicited Association of Clinical Research Professionals (ACRP) members to evaluate a recent trial as to the quality of the study and then how CROs and sponsors were performing on these key drivers of clinical trial quality. Finally, we created a statistical model to give the appropriate weight to each of these quality drivers.

Trials in which the site had a direct relationship with the sponsor were perceived as being higher quality compared to when the site relied on a CRO. The most critical driver of trial quality from the sites' perspective was communication—being available for questions, timely responses, and being helpful in resolving problems. While sponsors and CROs are doing reasonable well in this area, improvements in communication will yield the greatest benefits to improving clinical trial quality. Other significant drivers of quality from the sites perspective included the quality of the protocol, budgeting processes, technology, and monitor performance.

The results of this study illustrate a pathway by which sites, CROs, and sponsors can improve the quality of clinical studies. These findings can also provide a starting point for achieving an ROI on quality investments. Perhaps, most importantly, the results of this study give clinical trial sites a greater opportunity to provide insights into quality improvement methods for the clinical research enterprise.

The mission: Improve site support

Clinical trial sites are the underappreciated foundation of the medical research enterprise.[1] Despite this importance, sites struggle to execute studies effectively and efficiently.[2] But sites depend on sponsors and CROs to support them by providing services and resources that allow them to execute the study plan. This lack of support can contribute to trial delays, increased costs, and considerable site turnover.[3] As a result, investigative sites are becoming a scarce resource that limits the ability to conduct clinical research.[1]

The purpose of this paper is to address this situation by identifying the things that sponsors and CROs do that allow sites to execute high-quality clinical trials. Clinical studies depend on multiple stakeholders—often broken into separate organizations—working together effectively to coproduce a high-quality research program. Coproduction refers to the phenomenon by which multiple actors must apply their knowledge, skills, services, and resources to

cocreate a complex service.[4] While the site may interact with the patient, delivering a high-quality clinical trial depends on sponsors, CROs, and sites working collaboratively.

But there are potentially thousands of coproduction activities that could impact trial quality. What are the specific drivers that lead to higher quality clinical studies? We distill all of these issues into the three RQs mentioned.

RQ1: What are the coproduction activities that sponsors and CROs provide to sites that lead to high quality trials?

To examine RQ1, we conducted two focus groups of 12 to 15 study coordinators each at the 2015 ACRP national conference in Salt Lake City, Utah. We had no difficulties recruiting potential subjects. Clinical research professionals were anxious to participate. Several of the participants told us that they were delighted they could contribute "so our voices could finally be heard."

Our approach to these discussions was inductive. The participants all had about 10 years or more of trial experience, so their observations were naturally granular. Each of the sessions was opened by asking, "What are the things (or activities) that sponsors/CROs do that help you execute a high quality study?" This led to a long list of performance activities. The process was iterative as participants clarified and built on each other's observations. Once we had collated this list of performance activities, we worked with the focus groups to organize all of them into the following eight distinct groupings:

- Protocol
- Budgeting
- Initiation
- Monitors/CRAs
- Closeout
- Reimbursement
- Communication
- Technology

We tested these groupings with focus group members by challenging, for example, whether budgeting and reimbursement were really different groups.[5] Once we confirmed that these were distinct groups and aligned the items within each one, we arranged the participants into subgroups of about three people each to organize the items. At the end of the session, each group presented their refinements and the larger group commented on their work.

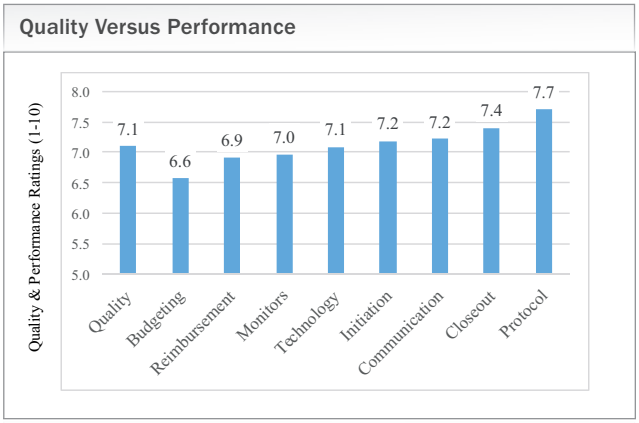
Representative items—framed in survey format—for each category are shown in Table 1. We also included a set of questions to assess the quality of the clinical trial from the site's perspective, which served as the dependent variable, shown at the bottom of Table 1 and derived from the SERVQUAL measure.[6,7] All of these items were edited for clarity, combined with similar items when appropriate, and loaded into the CRO Analytics' Performer platform in preparation for a survey.

Quality Drivers

ITEMS	SURVEY FORMAT
Protocol	Rate the complexity of the protocol. Please evaluate the protocol as to being well-organized, reasonable inclusion/exclusion criteria, etc. How responsive were they to questions you had about the protocol? As to protocol amendments, please rate the: • frequency of protocol amendments. • appropriateness of amendments. • providing money and budget support for amendments.
Budgeting	Their budgeting procedures permitted adequate resources for this trial. They paid us fairly for addressing SAEs, protocol amendments, etc. Did the budget allow for realistic time for coordinators?
Initiation	Rate the investigator meeting. They provided timely supplies (e.g., drugs, equipment) needed for the study. They provided adequate money and resources for recruiting subjects.
Monitors/CRAs	They were organized and prepared for site visits. They were respectful of our time. They acted as an advocate for us. They understood the protocol. Rate the turnover of monitors in this study.
Queries	Requests for queries were appropriate. Their helpfulness in resolving queries. Their fairness in adjudicating queries.
Closeout	Rate their performance on closeout visits. Rate their performance on drug reconciliation.
Reimbursement	Payments were accurate. Payments were adequate for the demands of the trial. Payments were on-time.
Communication	They provided information in a timely fashion. They were available for questions. Overall, how helpful were they in resolving problems?
Technology	Their technology was easy to use. Support was available for resolving issues with the technology. Please evaluate the CTMS system.
Overall Quality	Rate the overall quality of the trial relative to your expectations for this trial. They were very skilled at conducting clinical trials. They delivered on their promises They were always ready to help us in this trial. They gave us confidence in their ability to conduct this trial. They treated us as a partner in the research process. They had high quality materials and technology. When they promised us something, they got it to us on-time. When we needed something changed, they tried to accommodate us. They treated us as if our site was important to the trial.

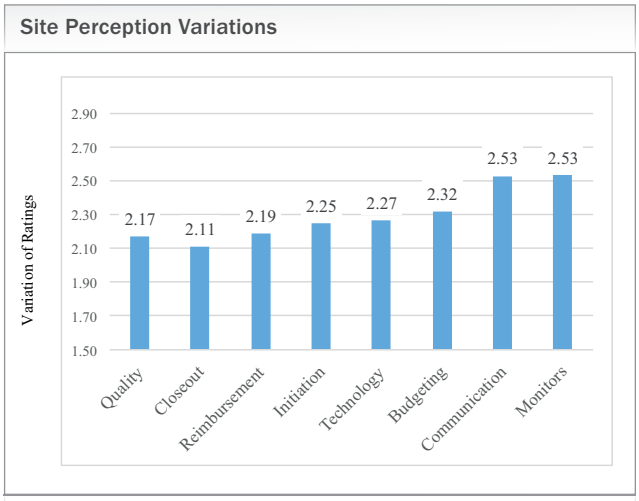
Source: Howley et al.

Table 1. Representative items within each of the performance areas.



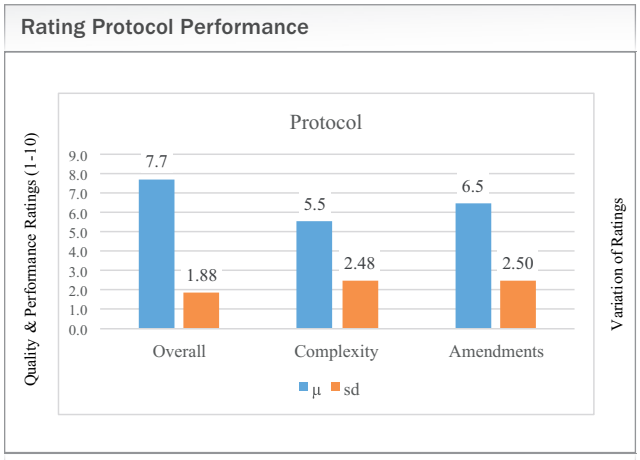
Source: Howley et al.

Figure 1. Site perceptions of quality and performance (means).



Source: Howley et al.

Figure 2. Amount of variation in site perceptions of quality and performance (standard deviation). Greater variation means less consensus on the performance.



Source: Howley et al.

Figure 3. Site perceptions of protocol performance drivers.

RQ2: How do sites evaluate sponsors and CROs on these key drivers of quality?

We solicited responses from the ACRP membership, excluding those members who participated in the focus groups. Respondents logged on to the Performer tool. They were instructed to think about a Phase II or III trial that completed recently and then to evaluate the items with that study in mind. We also asked them about characteristics of the trial and demographic items.

We received a total of 278 responses from experienced research professionals. The respondents had an average of 10.7 years' experience. About 94% of respondents characterized themselves as clinical trial coordinators or clinical research managers, with 3% describing themselves as principal investigators and 3% using a variety of other job descriptions (e.g., consultant). The trials involved various therapeutic areas. Cardiology only made up 8% and oncology 3% of the trials. Most of the studies were Phase III (75%); the rest (25%) were Phase II. The average trial consisted of 70 subjects (sd= 495), with a long right tail. Eighty percent of the studies in this sample met their enrollment goals, higher than typically reported.[8]

How did sites evaluate the overall quality and performance in the coproduction activities? The average overall perceived quality of the clinical trials was 7.1 (sd= 2.17) on a scale of 1 to 10 (1 = low quality; 10 = high quality). This average is high compared to similar studies we have conducted on clinical trial quality. Figure 1 illustrates the overall quality ratings with the ratings for each of the performance areas. This graph is constructed so that quality is the first column on the left and then performance areas are ordered from least to greatest (left to right). Each of the performance areas demonstrated discriminant validity from the others, meaning that we demonstrated statistically that budgeting was distinct from reimbursement and all the other groups.

It is not surprising, given our focus group discussions, that budgeting, reimbursement, and monitors were the lower-ranking performance areas and that communication (μ= 7.2) and protocols (μ= 7.7) were rated more highly. Given these averages, we next sought to identify the amount of variation with each of these averages. Are these ratings consistent, or is there wide variation around this average? Greater variation means that there is less consistency or agreement about the quality and performance ratings. We screened for variation by looking at the standard deviations. A high standard deviation would indicate significant variation in the responses around the average. Figure 2 illustrates the findings on variation and standard deviations. Items with the highest standard deviation scores have the highest amount of variation (or less consensus) around that average (i.e., they are likely to have subgroups of very low or very high scores). Items with the lower standard deviation scores have less variation (greater consensus). Communication (μ= 7.2) has a relatively high rating, but there was also a lot of underlying variation (sd= 2.53) around that rating. This suggests that while many sites are rating communi-

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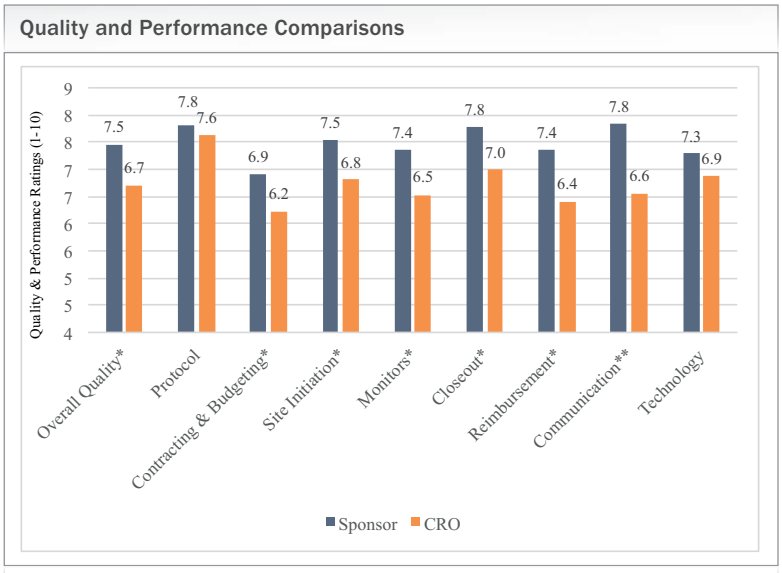


Source: Howley et al.

Figure 4. A comparison of sponsors vs. CROs in performance and quality ratings.

cation very high, there is a lack of consensus about this performance metric.

The findings regarding the protocols were more complex. In examining the means and variation of the ratings of the protocol sub-drivers, we found that some of the important ones—complexity of the protocols and the frequency of amendments—had low ratings with high variation, or a lack of consensus. This is a paradoxical finding: even though the sites rated the overall quality of the protocols highly, they thought they were exceedingly complex, with excessive amendments. We also found that the correlations between overall protocol quality to the complexity (r= .05) and amendments (r= .26) were very low.

There is a disconnect between how sites evaluate the quality of a protocol and its complexity and amendments. We interpret these findings as an example of lowered expectations. It may be that sites have simply accepted the complexity of protocols and frequent amendments as a norm, so it does not impact their ratings of the overall quality of the protocol (see Figure 3 on page 24).

Finally, we found that sponsor companies outperform CROs in overall quality and many performance areas, as shown in Figure 4. Labels that have a single asterisk (*) were found to be statistically significant at p= .05 in a multivariate ANOVA (analysis of variance) and the labels with a double asterisk (**) were significant at p< .001. We see two possible explanations here based on our focus group discussions. It may be that CROs are conducting a wide variety of studies with many different sites, thus an individual site does not feel like it is getting the support or attention from the CRO. It may also be that the CRO can be perceived as a "middle-man" that blocks or delays the site from the getting information or support it needs to execute the study. Further research is needed on this question.

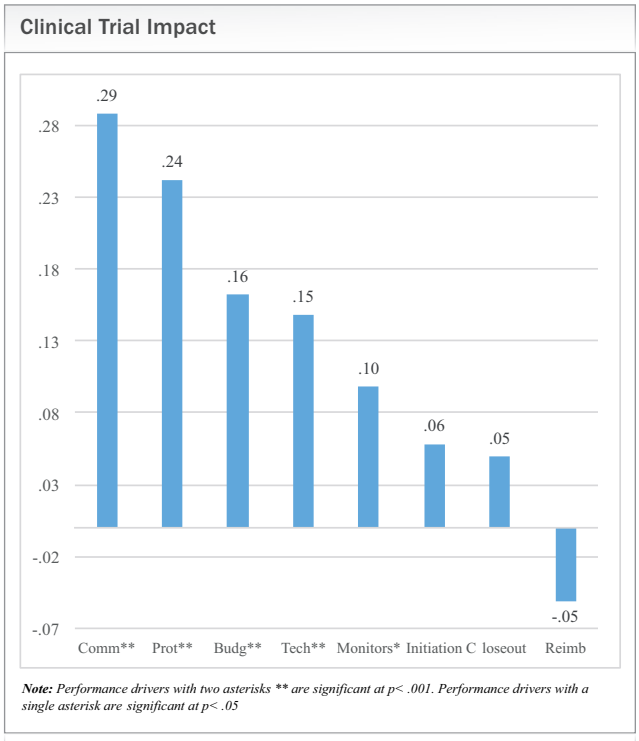
RQ3: How do each of these coproduction activities drive clinical trial quality?

To this point, we have assumed so far that each of the performance drivers all have an equal impact on quality. To drill down further and weigh the relationships between overall quality and the eight performance areas, we created a multivariate linear regression model. The sites' perception of the quality of the trial was the dependent variable and the performance areas were the independent variables. We also included a set of covariates—variables that might influence the relationship between trial quality and performance—in the model. The covariates were the size of the trial (number of subjects); whether it met its enrollment goals and endpoints; the complexity of the protocol; the appropriateness of protocol amendments; whether the site's contract was with a sponsor or CRO; and the length of the experience in clinical trials of the respondent.

The regression model explained a statistically significant (F(15,244)= 48.5, p< .001) amount of variance (R2= .75) in clinical trial quality. The model met all of the regression assumptions and variable were centered to enhance interpretation. The coefficients with their statistical significance tests are shown in Table 2 (see page 28). We compare the magnitude of the coefficients graphically in Figure 5 (see facing page). In interpreting the coefficients, each of the variables was mean-centered before running the model. Each coefficient gives an estimate of the unique impact of that variable on trial quality at the mean of all the other variables. Also, the variables for total subjects and years' experience were skewed to the right and, thus, were log-transformed.

There is a disconnect between how sites evaluate the quality of a protocol and its complexity and amendments. We interpret these findings as an example of lowered expectations.

The impact of the performance drivers on clinical trial quality fall into three distinct layers. In the top, most impactful layer, communication (b= .29, p< .001) and protocol quality (b= .24, p< .001) had the single greatest effects on quality in this study. Communication in common usage is usually a very broad term. The results from our focus groups offer drill-down insights. In the focus groups, sites mean very specific things when they speak of communication. When a study team is communicating well, that means that they provide information in a timely fashion; are available for questions as they arise; and are



Source: Howley et al.

Figure 5. The magnitude of effect of the performance drivers on clinical trial quality.

available and helpful in resolving problems. The impact of protocol quality is particularly impressive because we included protocol complexity and amendments as covariates in the model. Protocol quality has an impact on trial quality above and beyond complexity and amendments.

In the middle tier of performance drivers, budgeting (b= .16, p< .001) and technology (b= .15, p< .001) had statistically significant and positive—although more moderate—impacts on trial quality. Budgeting refers to the process of establishing the resources for the site's services. Within this category, fairness was the dominant theme. The recurrent theme that we heard in the focus groups was that site coordinators simply wanted to be paid for the requested work. They become very frustrated when the site must absorb the cost of adjusting to protocol amendments, training new monitors, handling serious adverse events (SAEs), or just budgeting extra time for the coordinator to do the work demanded by the protocol. Notice that this budgeting driver is distinct from the actual reimbursement, which was not a significant driver.

Within the technology areas, sites often struggle with multiple clunky software systems that are not integrated. On average, attendees at the focus groups had to separately log into six or seven technologies for each trial. Sites want seamless, integrated trial technologies and improving technology will have significant and substantial effects on perceived clinical trial quality. Improving technology will have a significant, though moderate, impact on trial quality.

The performance of the monitors (b= .10, p= .02) had a slightly less substantial, but still significant impact on clinical trial quality. Sites described in the focus groups that they want monitors who can serve as a resource to help them execute trials better and more efficiently. Inexperienced monitors—that the site must train—who don't understand the protocol and are disruptive to site operations are an ongoing frustration for sites.

Site initiation (b= .06, p= ns), closeout (b= .05, p= ns), and reimbursement (p= -.05, p= ns) were not significant performance drivers of quality in this study. Even though closeout has a negative coefficient, it is not statistically different from zero. In understanding these results, remember that this model estimates the unique effects of each performance driver, exclusive of all the other performance drivers. So if it seems like initiation (or closeout or reimbursement) should have been significant, remember that we are estimating the isolated effects of initiation on quality, excluding the effects of communication, the protocol, budgeting, technology, and monitors.

Conclusion

Sites are the foundation of the clinical research enterprise, but they have surprisingly little input in the development or planning of trials. The purpose of this research was to provide sites the ability to give their perspective of how we can improve the quality of clinical trials. The recurrent theme that we find in both the focus groups and statistical analysis is that sites are looking for partners who can help them serve their patients and conduct excellent science. Their common experience is that they often struggle to be treated fairly.

The recurrent theme that we find in both the focus groups and statistical analysis is that sites are looking for partners who can help them serve their patients and conduct excellent science.

The results of this research may not surprise those who work with sites. This data has been anecdotally available for some time. The real contribution of this study is not only in the systematic collection of all of the performance drivers, but, more importantly, in giving weights to each of these performance drivers. In doing so, we are able to think about an ROI on site relations.

Suppose you are a sponsor or a CRO that wants (or needs) to improve site relations. The results of this study provide a way for sponsors and CROs to assess where they stand compared to the rest of the industry. Companies can send out a survey and compare their results to the data illustrated in this report. Based on the results of their survey, companies can think about the ROI on investing to improve their scores using the results of the regression model.

Coefficients at a Glance

		Coeff	Std Err	t	Sig.
	Intercept	7.37	.25	29.65	.00
MAIN MODEL					
	Communication	.29	.05	5.35	<.001
	Protocol	.24	.05	4.87	<.001
	Budgeting	.16	.05	3.34	<.001
	Technology	.15	.04	3.73	<.001
	Monitors	.10	.04	2.38	.02
	Site initiation	.06	.05	1.16	ns
	Closeout	.05	.05	1.03	ns
	Reimbursement	-.05	.05	-1.05	ns
COVARIATES					
	Total subjects	.22	.14	1.60	ns
	Years' experience	-.19	.09	-2.10	.04
	Protocol complexity	-.07	.03	-2.40	.02
	Contract sponsor/CRO	-.05	.15	-.35	ns
	Protocol amendments	.01	.03	.35	ns
	Met enrollment goals	.14	.19	.69	ns
	Trial met endpoints	-.01	.15	-.07	ns

Source: Howley et al.

Table 2. Model regression coefficients with significance tests.

Suppose a company's survey shows that it rated a 6.5 on a 1-to-10 scale for communication and a 7.0 on overall quality. Congratulations—not a bad score. But if one looks at our data, they will see that our sample rated an average of 7.2 for communication. This means that the organization would have room to improve in this area. Is it worth investing to improve communication? To assess this question, examine the results of the regression. Communication had a coefficient of .29. That means that if a sponsor or CRO invests in communication and is able to raise its communication rating from 6.5 to 7.5, it would improve its quality score from 7.0 to 7.29. What specifically does one look at to improve communication? Examples of the subdrivers are found in Table 1.

Now imagine that a company's survey shows a 5.5 for closeout and it is compared to our findings of 7.4. The rating gap is fairly significant. Should a company, therefore, invest to improve its closeout ratings? The results of our regression model would suggest no. The closeout driver had no significant effect on quality, so the results of this study would suggest an organization's investment would be wasted. The firm certainly might make some non-monetary investments using guidance from Table 1, but it would not improve quality by investing heavily in this area.

Several limitations should be kept in mind in evaluating the results of these studies. First, some might argue that the ACRP membership is not a representative sampling. Someone who belongs to a professional organization like ACRP, attends the national conference, and even volunteers for a focus group is likely to be more engaged in their professional work that the average site coordinator. While this is possible, we would also point out that these are also likely to be key opinion leaders within the profession—the very group that sponsors and CROs need to reach in order to improve clinical trial quality.

We would also note that the model estimates are general across a variety of therapeutic areas and phases of clinical trials. Although we would argue that these estimates would generalize across clinical studies, estimates may vary around our means within specialty areas.

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Michael J Howley, *PA-C, PhD, is Clinical Professor, LeBow College of Business, Drexel University, email: mikehowley@drexel.edu;* ***Peter Malamis*** *is CEO, CRO Analytics, LLC, email: pmalamis@croanalytics.com;* ***Jim Kremidas*** *is Executive Director, Association of Clinical Research Professionals (ACRP), email: JKremidas@acrpnet.org*

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Making the Most Out of Enrollment Rescue Dilemmas

Pete Fronte, Beth Harper

Survey uncovers key best practices that sponsors, CROs, and sites should consider when faced with patient enrollment challenges.

PEER REVIEW

Studies in "enrollment rescue mode" present dilemmas for sponsors, contract research organizations (CROs), and sites alike. While the sponsor ultimately has the most to gain or lose if a trial fails to achieve its enrollment goals, there are several ramifications to the study site that are often not considered. Sites invest a lot of time and resources to get up and running only to find that the trial is difficult to enroll or is ultimately terminated.

This "enrollment rescue dilemma" and how sites face these challenges is the focus for this article. Since so little is known about the impact of enrollment rescue from the site's perspective, the authors conducted a survey to gain a better understanding of the nature and frequency of these situations. While the ultimate goal is to avoid rescue altogether, when it does occur all parties need to do things differently. This article will explore how sites tackle enrollment rescue situations, and provide some best practice considerations for how both sponsors and sites can make the most of these circumstances.

Frequency and root causes

For the purposes of this article, we define enrollment rescue as studies that are sufficiently behind in enrollment. More specifically, the particular scenario we'll explore is the rescue study in which the enrollment target has or will be missed, resulting in more sites being added, funds being provided to sites for local tactics, and/or central media campaigns added in the hopes of reaching the enrollment goal at some point beyond the original target date.

It's easy to cite the often-quoted statistics from the Tufts Center for the Study of Drug Development (CSDD) when it comes to the percentage of sites that don't enroll or the number of trials that are delayed from an enrollment perspective.[1] Among other statistics, the 2012 Tufts CSDD study reported that 53% of studies had extended timelines, with one of six studies taking more than twice as long as originally planned. In a 2015 article about an extensive analysis of clinical trial enrollment, the authors report that (19%) of the trials analyzed either terminated for failed accrual or completed with less than 85% expected enrollment, seriously compromising their statistical power.[2]

From a failed enrollment perspective, there are literally over 150 root causes as to why sites don't meet their enrollment goals.[3] Broadly speaking, these can be grouped into protocol, patient, site, sponsor, or site relationship management related issues. Communication problems among stakeholders, patient enrollment delays, overly complex protocols, and poor site compliance are just a few of the many reasons why rescue action is needed.[4]

Based on Altura's experience supporting recruitment for over 300 studies, recruitment planning tends to focus on asking sites how much they can enroll during the site selection process. This site estimate on the internal potential subjects is coupled with external supply estimates typically from sources such as central media campaigns and/or pass through local recruitment funds. This process frequently leads to an overestimation of enrollment potential, resulting in an increased probability of a future rescue scenario.

Even with the best intentions and a committed study team, sites are over worked and understaffed, as highlighted in the findings from a recent industry survey (see Table 1 on facing page).[5] This further compounds the challenges that even the most well-intentioned sites face.

Typical approaches to a rescue

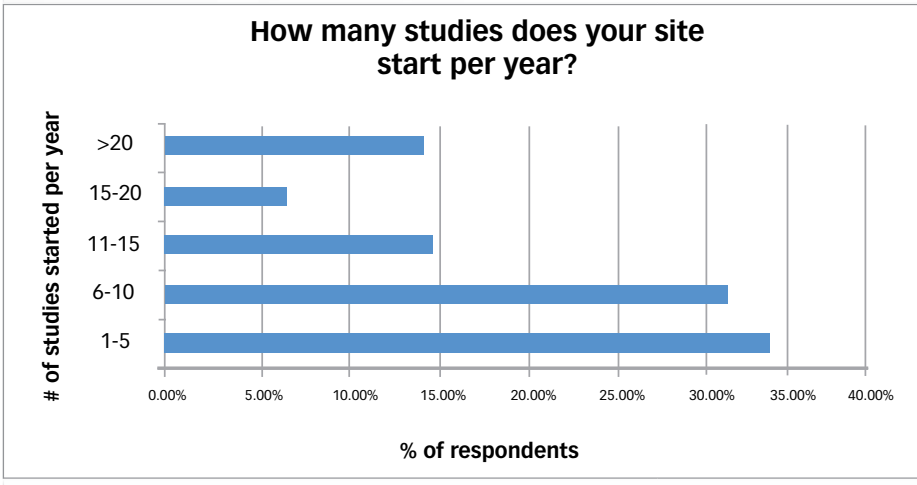
Consider what typically happens in the enrollment rescue scenario. The sponsor or CRO usually undertakes the same site feasibility, qualification, and selection process for add-on sites that they followed initially and/or they decide to add central or local tactics and resources. If sponsors don't adapt their approach, they may still end up with non-performing sites.

Adding incremental resources for current sites can also be a challenge, as most sites may be experiencing study fatigue. If new tactics are brought in (including local or central), then vendor additions or integration can also be a challenge for sites. Increased volume of patients that do not meet criteria can further increase a site's study fatigue and exhaust their limited resources on unfruitful efforts.

From the site perspective, if the new sites aren't judicious about evaluating rescue situations, they may not be successful, thus putting their reputations at risk. If a site fails to enroll ample subjects, then they can't leverage study startup costs (e.g., preparation and training for investigators and study staff) and may be financially worse off as well.

How discriminating the new sites are when evaluating these studies, what they ask for, and what influences their decision are among the topics explored in a survey the authors undertook to better understand how sponsors, CROs, and sites alike can maximize these situations.

Trial Initiation



Source: Fronte, Harper

Figure 1. The average number of new studies started per year.

Survey methodology and findings

Research sites from various specialties within the U.S. and Canada were identified via a database of sites with whom Altura has worked over the past 15 years. Since its inception in 2000, Altura's mission is to expand study participation by involving more patients, healthcare providers (HCPs), and health systems via its Study Engagement Platform™, which includes HIPAA-confirming technology such as its HCP Studies™ mobile app/portal. A total of 323 sites responded to an online survey in the fall of 2016 to determine enrollment rescue insights and experiences.

Chief Challenges for Sites

Increase in workload	61%
increased complexity of duties/responsibilities	59%
downsizing of dept. staff	22%
Increase in learning new clinical trial tech	18%
Tech not adequate to current responsibilities	16%
Downsizing of related dept. staff	14%
Increase in global trials	11%
Increase in outsourcing relationships	10%
Have not faced any challenges this past year	7%
Don't have the knowledge/exp to perform	6%
Decrease in outsourcing relationships	4%
Other	13%

Source: CenterWatch, Association of Clinical Research Professionals (ACRP)

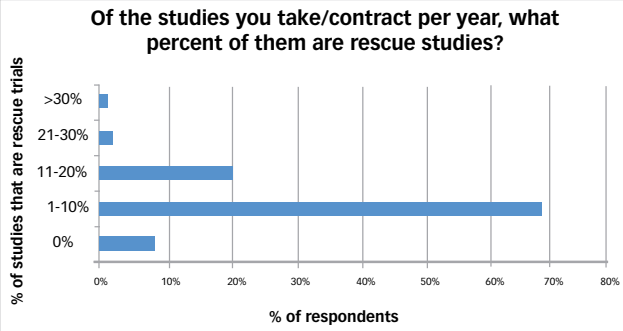
Table 1. Top challenges noted in CenterWatch-ACRP Career and Salary Survey (N=2,508).

From the site perspective, if the new sites aren't judicious about evaluating rescue situations, they may not be successful, thus putting their reputations at risk.

To gain an understanding of how frequently sites are faced with evaluating rescue study opportunities, sites were asked to indicate their total number of study starts per year along with their estimates of the percentage of those that are rescue situations. On average, the majority of respondents start one to 10 trials a year (see Figure 1).

Of these trials, on average, less than 10% of the trials the sites contract with are rescue studies. This roughly translates to about one rescue trial that the survey respondents take on each year (see Figure 2 on page 32).

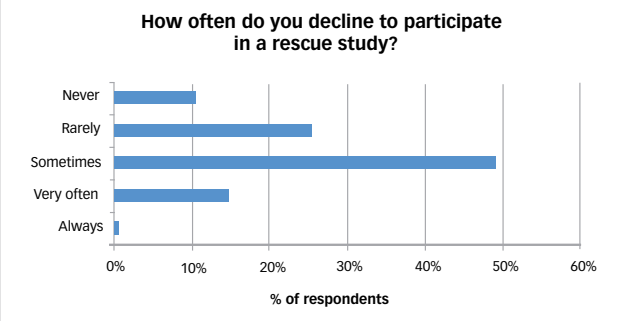
'Rescue' Frequency



Source: Fronte, Harper

Figure 2. The percent of studies contracted per year that are rescue studies.

Rescue Go/No-Go



Source: Fronte, Harper

Figure 3. The frequency of sites declining to participate in a rescue study.

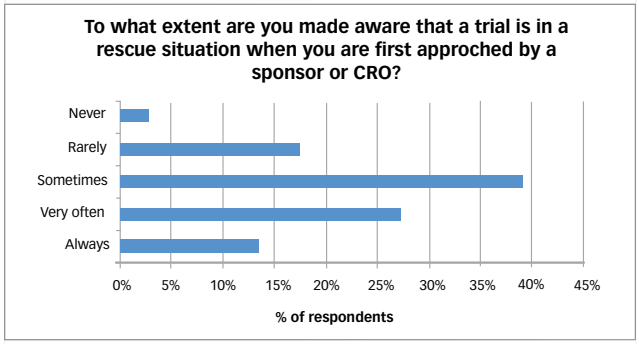
Interestingly, for the most part, when the sites are approached about a rescue opportunity, they typically sign on for the trial (see Figure 3). This may reflect a general phenomenon for sites overall; they optimistically accept all trials regardless of whether issues about enrollment or other challenges are known upfront or not. The psychology of sites accepting protocols and sponsors/CROs accepting sites for which they are not well suited likely contributes to the chronic problem of rescue studies in the industry and warrants further exploration.

On the other hand, the survey results revealed that sites are not always made aware, up front, that a study is in rescue mode (see Figure 4). Not being aware of the situation can certainly impact the site's enrollment performance, so it behooves all parties to thoroughly assess the situation before making a commitment to participate.

When sites are made aware that a study is in rescue, they report a myriad of variables that they assess before making the decision to accept the trial. The availability of the patient population and ability to successfully enroll was by far the primary factor sites considered when taking on a rescue project (see Figure 5).

The majority of the survey respondents noted that they are only

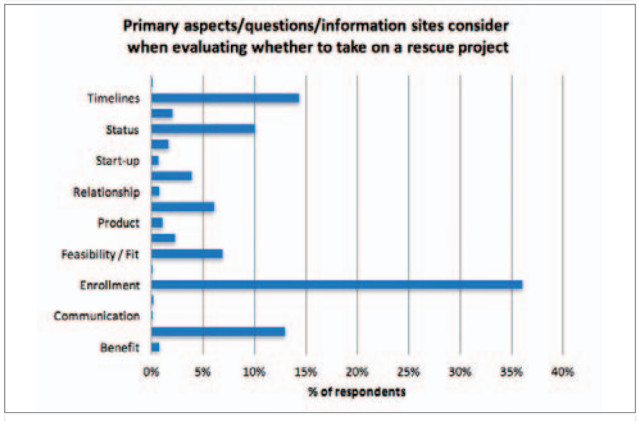
Sites Clued-in?



Source: Fronte, Harper

Figure 4. The extent to which sites are made aware that a trial is in a rescue situation.

Pre-Rescue Considerations



Source: Fronte, Harper

Figure 5. The most important variables that sites assess when considering taking on a rescue study.

sometimes made aware of the specifics, with about 20% reporting that they are rarely or never made aware of the details (see Figure 6 on page 34). Whether this is an obligation of the sponsor to reveal this, or the site to demand this information, may be a matter of debate. Nonetheless, without a detailed understanding of the factors leading to poor enrollment, the add-on sites are at risk for performing the same or worse than the existing sites.

Regardless of how much information about the enrollment challenges is received or revealed, the survey respondents noted that they only receive additional support in about 25% of the cases. The majority of time the sites report receiving only the same level of support from the sponsor/CRO, as in a non-rescue situation (see Figure 7 on page 34). Sponsors and CROs may be missing a golden opportunity to set the add-on sites up for maximum enrollment success. Above and beyond this, it's also critical to address the needs of the current sites who may need some support, without abandoning them altogether in favor of adding on additional sites.

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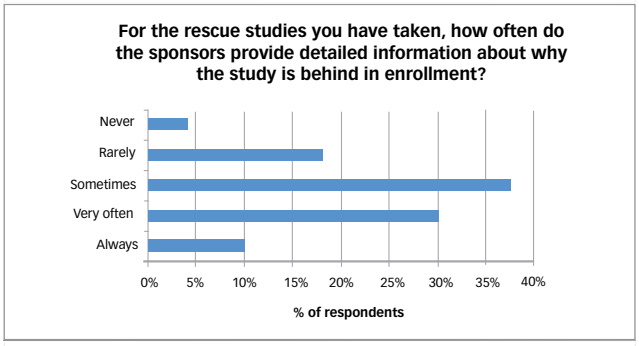
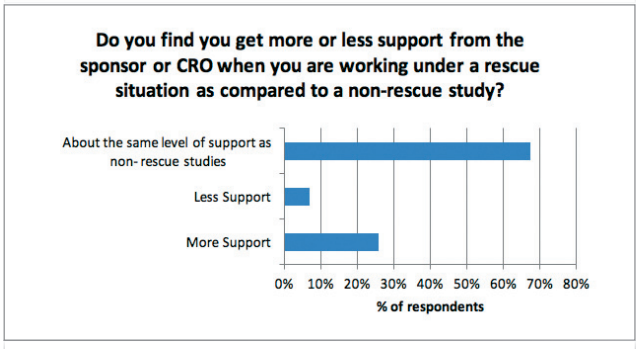
Relaying Reasons for Rescue



Source: Fronte, Harper

Figure 6. The extent to which the sponsor provides detailed information about the reason for poor enrollment.

Support Levels



Source: Fronte, Harper

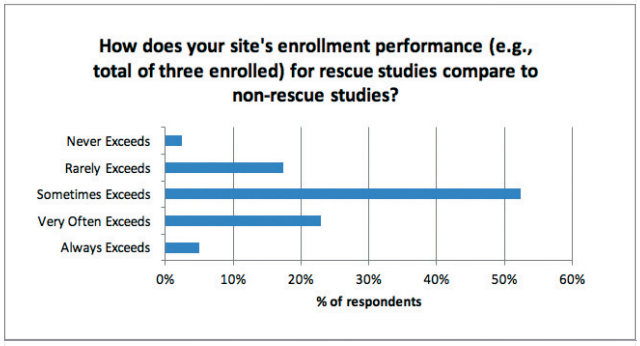
Figure 7. The level of support the sites report they receive from the sponsor/CRO in a rescue situation.

The vast majority of survey respondents indicate that their patient enrollment in these clinical trials sometimes exceeds enrollment in the non-rescue situation, with about 20% of the sites indicating their performance rarely or never exceeds that of the non-rescue situation (see Figure 8). It should also be noted, however, that the target is frequently lowered for rescue sites, which makes it easier to achieve the enrollment goal. Furthermore, protocol amendments may make entry criteria a bit easier in many of the rescue situations as well.

Whether additional support would have a significant impact on the site's enrollment performance may be difficult to quantify; however, intuitively, it makes sense that helping the add-on sites would lead to even better performance. The same would apply to current sites. When asked about the type of support that would promote a more successful collaboration in rescue situations, sites reported a number of areas where they feel sponsors and CROs could be more helpful (see Figure 9 on facing page).

Not surprisingly, being transparent about and addressing all of the root cause issues contributing to the rescue situation ranked highest in terms of ensuring success in these situations.

Enrollment Output



Source: Fronte, Harper

Figure 8. Sites' reported enrollment performance for rescue studies compared to non-rescue studies.

Make the most out of a rescue situation

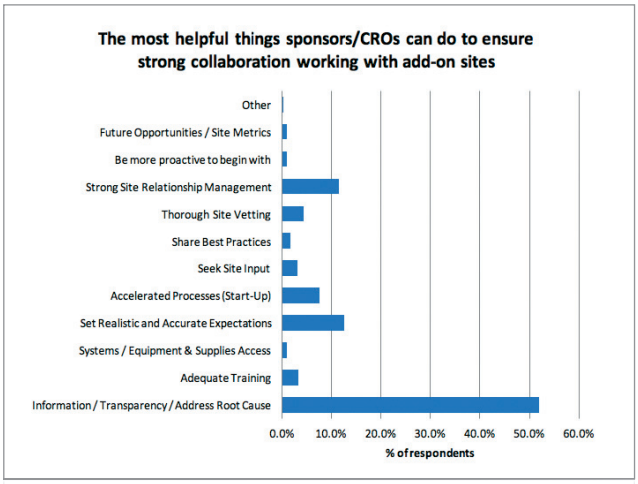
Based on self-reported results, the majority of sites who take on rescue studies have some success in enrolling for them; however, they may be even more successful with some additional transparency and support. The right type and amount of support for current sites would also be beneficial. Most sites want to understand the challenges ahead of them through full disclosure about the successes, study issues, and timeline constraints. Sponsors and CROs could improve in these areas, as only 41% of the surveyed sites are always or very often made aware that a trial is in a rescue situation when first approached by a sponsor or CRO. Furthermore, sites report that sponsors provide detailed information about why the study is behind in enrollment very often or always only about 40% of the time.

> Since enrollment at sites tends to be serendipitous, it behooves sponsors to identify sites that have strong potential but just do not have the tools and time to focus on enhanced recruitment.

With the pressure of finding patients in a shorter timeline in rescue studies, sponsors need to recognize that sites need and will benefit from more support, particularly in the area of recruitment support. With the majority of the sites (~70%) reporting they received about the same level or less support from the sponsor or CRO when working under a rescue situation as compared to a non-rescue study, this presents a major opportunity for improvement.

Adding more sites can be a solution, but the sunk cost with existing sites is significant. Since enrollment at sites tends to be serendipitous, it behooves sponsors to identify sites that have strong potential but just do

Boosting Rescue Performance



Source: Fronte, Harper

Figure 9. The top recommendations for promoting a more successful collaboration during rescue situations.

not have the tools and time to focus on enhanced recruitment, especially for studies with stringent entry criteria where a wider but focused net must be cast. Examples of tactics for current sites, and new rescue sites, include:

- Gain access to site and site-related electronic medical records (EMRs) and databases to validate true enrollment potential and drive efficient patient prescreening.
- Gain access to HCPs that are in the care continuum for the desired population and ensure they have easy access to the study and patient transfer process.
- Ensure all central and local media leads have been reconciled and processed.

Sites share an equal responsibility for ensuring a successful collaboration in rescue situations. Some specific best practices and questions the sites should consider include the following:

- Compare the study's challenges with your site's experience in similar trials. Is your site going to be able to overcome what is a challenge for other sites?
- How will the site find the patient (e.g., databases, provider referrals, principal investigators practice patients as they present, media)?
- What are the studies top three prescreen disqualifiers and screen fail reasons? How does this impact your patient pool?
- If you aren't able to recruit from your known patient population or a well-established referral base, how much and what type of recruitment support (e.g., budget, recruitment service provider) will be available to help you reach the target population?
- Have you taken studies like this in the past? Did you succeed in meeting your goal? If not, how will this study be different?
- From a budget and contractual standpoint, are there any obvious issues that will preclude you from a rapid start-up? Will the budget cover your start-up expenses and efforts in the event enrollment is met or the trial is terminated before you actually get initiated?
- Do you have the staff and resources to dedicate to the trial and are they willing and able to work within the additional pressure inherent in a rescue situation?
- Logistically, can you conduct the study visits and procedures with the space, time, and staff that you have?
- Are any of the inclusion/exclusion criteria ambiguous and/or subject to interpretation? If so, clarify your position with the sponsor to ensure alignment.
- Have protocol amendments occurred or will they occur? What's the anticipated impact?
- If central or local media will be implemented, what type of support will be provided to ensure site burden is minimized.

Summary and conclusions

While rescue situations may be an inevitable fact of life for the clinical trials industry, the results of this survey highlight important and actionable insights that sponsors, CROs, and sites should consider when faced with enrollment challenges. It's important not to assume all current sites can't increase enrollment with the appropriate resources and support. At the same time, it might be time to close many current sites if indeed they have no additional potential to enroll. For add-on sites, being forthright about the fact a trial is in rescue, sharing as much information about the causative factors and what's being done to address these can all have a significant impact on ultimately achieving the enrollment goals. The fact is that all study stakeholders share an important role in ensuring enrollment rescue success.

> Since enrollment at sites tends to be serendipitous, it behooves sponsors to identify sites that have strong potential but just do not have the tools and time to focus on enhanced recruitment.

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Pete Fronte *is President and CEO of Altura, email: pfronte@alturastudies.com;* ***Beth Harper*** *is President of Clinical Performance Partners, Inc.; email: bharper@clinicalperformancepartners.com*

Improving the Traceability of the Clinical Trial Supply Chain

Darryl G. Glover, Jan Hermans

Outlining the benefits of using blockchain technology across the supply chain to more securely record and distribute data to sites.

PEER REVIEW

The Drug Supply Chain Security Act (DSCSA) and similar global regulations[1] were designed to help protect the integrity of the medication supply chain by gathering data at each step of a medication's journey. While the focus is on the "Approved Drug" supply chain, there has been little conversation or focus on the clinical drug supply chain.

Blockchain technology has the potential to positively impact clincal trial supply chains by improving the traceability of medications from active pharmaceutical ingredient (API) to patient, while facilitating the gathering of patient-level data in a HIPAA-compliant manner. This is done by having patients and other individuals participating in the network record data to the blockchain, which then moves that information to the appropriate system and groups with access to view that data. The data is auditable, immutable, and can help create a longitudinal record of a patient's health status.

Blockchain overview

What exactly is the blockchain and how can it be applied as a track-and-trace solution for clinical trial medications?

To begin, let us define a few key terms related to blockchain technology[2]:

- **Distributed ledger:** A distributed ledger stores data, which is then housed on the systems of all trusted parties in a network. However, not all trusted parties can access all of the data.
- **Public/private key cryptography:** The keys control the way that information is accessed and encrypted onto the blockchain. This well-vetted and established technology, first developed in the 1970s, gives individuals or organizations access to data while validating their identity. Furthermore, these keys determine who can access or add information to the blockchain.
- **Consensus:** This is the mechanism by which all parties in a blockchain network validate that data being placed on the blockchain is from a trusted source/participant. This is done by computer systems using a cryptographic proof.
- **Smart contract:** These are executable pieces of code that perform a function, such as issuing a payment or transferring documents, when the conditions of a transaction are met. For example, a university has licensed its IP to a company and the content of the IP is made available once the licensing fee is received.

How does the blockchain work?

The blockchain is a distributed digital ledger, which immutably records data. This means that it records data and then disperses a copy of the information to the trusted partners in the network. This distribution, but not full access to all data held on the blockchain, has several advantages. Firstly, each participant in the network validates that the data being placed on the ledger is from a member of that network. This has the advantage that someone from the outside or without the right permission (public/private key combination) cannot add data to the blockchain. This creates the security and validation of the immutable records being created. The impact is that someone from outside of the network cannot introduce false information, such as false serial numbers, into the system or read data that they do not have access to. While most attacks (hacks) do occur by someone inside an organization, the fact

that an individual's identity and actions are tracked through the use of their public/private keys decreases this as a source of attack. The distributed nature of the ledger, ultimately, makes it impossible to make simultaneous changes to all copies of the ledger and is a further safeguard against both internal and external attacks.

While the blockchain is not as familiar as products from Google, Microsoft, or Apple, the technology behind it is quite well established, existing since the 1940s. The blockchain has just combined cryptography and public/private keys to create a "trustless" network (when the ability to trust the comprised systems does not depend on the intentions of any particular party). The blockchain, itself, has performed and carried out hundreds of millions of transactions securely since it was first introduced in 2009. Around 2014, the advent of smart contracts and improved transactions speeds began to occur as we entered the Blockchain 2.0 era.

There are two main reasons why an organization would want to implement the blockchain:

Data provenance is required for business or regulatory reasons and there is a requirement that this is recorded in a secure, immutable and, auditable manner.

- Bridging of internal or external IT systems is required in order to more easily move, gather, access, and view data holistically.
- While the initial applications of the blockchain focused on financial services, the concept of data provenance is being applied to fair trade goods, art, diamonds, designer clothing, solar energy and, the biopharma supply chain.

For the clinical drug supply chain, a root-cause analysis identifies three highlighted challenges that blockchain can resolve:

- **Traceability.** The chain between a clinical study sponsor, study patient, and site is long and involves the use of multiple IT systems. In a world where all parties involved are linked via a blockchain, it would be possible to leverage encryption and access control so that the members (trusted participants) could get confirmation of the receipt of the product without having access to protected patient information and, in turn, provides the ability to validate patient identity.
- **Assure completeness.** By introducing smart contracts, the entire clinical trial process can benefit from using blockchain technology. The process/trial milestones can serve as stage gates for the smart contract. The process will only proceed beyond that point when required actions are completed and correct.
- **Validity.** Before the initiation of a clinical trial, the sponsor must submit the parameters of the study to the appropriate regulatory authorities and various ethics committees (ECs) at the trial sites. At the study's conclusion, the sponsor's regulatory affairs department determines if all requirements have been fulfilled before accepting and then forwarding the results to the appropriate regulatory authorities for approval. The challenge that faces sponsors and regulators is how to ensure the validity of the data and to establish universal standards for that process. The implementation of blockchain technology can be the conduit through which such standards are implemented, since the validation and auditability of transactions are a core part of the technology.

Current trial supply chain challenges

Clinical trials are designed to assess drug efficacy. This process presents three challenges to any organization sponsoring or participating in a study:

- How to trace what product is in the packages?
- How to assure the correct data is collected?
- How to ensure that the study site does not become unblinded?

Several companies have adopted processes and applications to meet these challenges, but these are prone to human error. In practice, it often comes down to an individual validating the actions recorded in a software solution. Software systems, like interactive response technology (IRT) and randomization and trial supply management (RTSM), can assist yet lack the capability to validate events or transactions, like medication administration.

A fourth challenge is presented to the industry upon the completion of a trial and during the process of data collection:

- Are the results that have been collected complete and valid?

On the surface, this challenge can be easily negated; however, regulations, like the European General Data Protection Regulation (GDPR), will bring more scrutiny to this important area.

The following example can serve to make these challenges more tangible:

A few years ago, there was a Phase II study in Africa with a drug that was not stable at high temperatures. Because of this, it was important to ensure that the medication did not exceed a certain temperature. Upon examining the supply chain between plant and patient, this was quite challenging, as the placebo also needed to be preserved under the same conditions to prevent unblinding. Assuring this, in combination with providing the required documentation, proved to be an entire project by itself.

> While most attacks (hacks) do occur by someone inside an organization, the fact that an individual's identity and actions are tracked through the use of their public/private keys decreases this as a source of attack.

For this study, patients needed two different dosages at two different times. The physicians needed to confirm patient identity before administering the second dose. As many patients did not have photo identification, their identity was tracked using biometric data. The country's EC requested that the biometric data should not to be shared outside of the clinical sites. The general problem boiled down to one of traceability between the physical and digital world while assuring patient and data integrity—all key factors to conducting a successful trial.

This example demonstrates the complexity that can emerge in

one small part of a study. If that complexity is added to the entire chain, and also impacting external contract research organizations (CROs) and subcontractors, these challenges only grow exponentially. The blockchain becomes one key technology to alleviate these hurdles.

The other challenge is preventing patients from participating in multiple trials simultaneously while ensuring that contracted investigators, the data they enter, and the patients actually participating are consistent with the records at the various clinical trial sites. The introduction of biometrics can help ensure the integrity and security of the study and its drug supply chain. The Internet of things (IoT)[3]—a network of interrelated computing devices and mechanical and digital machines—then can help collect and transmit adherence data and assist with the detection of adverse events and the physiological effects of the investigational drug on the patient.

Regulatory considerations and potential

Regulations and application submission requirements can be viewed as a set of business rules that need to be adhered to—rules that can be managed on a blockchain. The regulatory audits and validation of the presented study findings and results is a slow, expensive, and labor-intensive activity. The introduction of the blockchain may alleviate this burden, as organizations can quickly demonstrate data validity due to the immutability of the records collected and the fact the authorities' specifications were incorporated and executed by the smart contracts implemented as part of that solution.

Applications from API to patient

API and comparator sourcing

An essential element of a clinical study is ensuring that that there is sufficient supply of the API to supply the trial. To produce enough API, multiple plants may be tasked or contracted. Because the drug is at an early stage of the development life cycle, the productivity of a single plant may be lower than expected. This risk of having an insufficient trial supply can be mitigated by making available real-time inventory to the study stakeholders up and downstream. This can be accomplished by having the information recorded and updated on a clinical study blockchain.

It is important to keep in mind that the API pilot plant has a critical role to play, as the API it supplies is the foundation upon which a clinical study report will eventually be submitted for review. The recording of this data on a blockchain then becomes the genesis record upon which all other data can be added and interconnected.

The core qualities of a model built on blockchain technology helps reach the high standards required of a clinical trial by providing integrity, analytics, and traceability. Having, from an early stage, a good overview of a producer's quality and ability to produce certain quantities of an experimental drug becomes an enabler to the study stakeholders.

Packaging

With the investigational drug product and comparator supply source secure, the next stage in a clinical supply chain is packaging. The creation of "smart packaging" (merging the physical and digital worlds) can generate new data for the sponsor to use. Not only can an organization encode the identity of the product allowing for traceability, but additional sensors can collect data from the moment the treatment is placed inside the package. All of this information can then be recorded to the blockchain to create a complete record of a medication's journey throughout the clinical study.

Storage and shipping

In a world where the rapid movement of goods is routine, the ownership of the drugs and authenticity becomes harder to trace in a physical world with shipping documents. When we enable smart packaging for drugs in shipment and storage, a more interesting picture emerges, where all products down to the individual blister level can be located and storage conditions assessed.

With an assurance of authenticity during the trial, in later large-scale production, similar serialization and tracking techniques across a trusted blockchain-empowered network can prevent counterfeit product from entering the supply chain.

Patient

The purpose of a trial is to track patients' responses to the investigatonal drug that was produced, packaged, shipped, and stored. At the end of the clinical supply chain, the data is provided to the sponsor for further analytics and analysis.

It is evident that the three core qualities of a blockchain model also improve the quality of data collected, along with its provenance. Again, it is the validating nature of the technology that benefits the patient, sponsor, and all other stakeholders.

Conclusion

Blockchain technology has many advantages in security, data protection, and the ability to bridge the disparate systems that manufacturers, CROs, and study sites utilize. This technology has the benefit of centralization without having all of the data located in one place, thus making it less vulnerable to external/internal attacks.

A combination of the process of serialization and blockchain technology holds the key to ensuring clinical trial integrity and to overcoming the challenges presented in this article. It provides an assurance that's missing in the industry today by leveraging the technology and knowledge of tomorrow.

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***Darryl G. Glover**, PharmD, MBA, is Chief Clinical Officer, iSolve, email: dglover@isolve.io; **Jan Hermans** is Business Unit Manager and Senior Consultant, CMAST*

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Shinal v. Toms: Informed Consent Must be Obtained by a Medical Doctor

Although there is evidence to suggest that medical doctors may not be the best-suited individuals to facilitate the informed consent process, it is likely to become the new normal for clinical research.

Darshan Kulkarni, PharmD, MS, Esq
Principal Attorney,
The Kulkarni Law Firm

The recent court case *Shinal v. Toms* involved a woman undergoing surgery to treat a benign brain tumor growing near the patient's pituitary gland. After discussing treatment options with Dr. Toms, then a neurosurgeon at Geisinger Medical Center's neurosurgery clinic, Mrs. Shinal spoke over the phone with Dr. Tom's assistant. The treating physician's assistant obtained an informed consent form from Mrs. Shinal prior to surgery. During surgery, Mrs. Shinal suffered permanent injury from complications and sued the physician, alleging his failure to explain the risks of and alternatives to her surgery.

Until *Shinal v. Toms*, physicians interpreted the duty to obtain informed consent as one that could be delegated to a qualified staff member, and to include talking with the patient, discussing an overview of the procedure in question, and ultimately obtaining the patient's informed consent. However, in *Shinal v. Toms,* the Pennsylvania Supreme Court found that effective informed consent stems from the contractual nature of the physician-patient relationship and, consequently, necessitated a "meeting of the minds" between the parties, which could only occur by a physical interaction between the doctor and patient. In support of its holding, the court quoted *Kelly v. Methodist Hospital*, noting that the physician's unique relationship with the patient, as well as the physician's education and training, mean that "the physician is in the best position to know the patient's medical history and to evaluate and explain the risks of a particular operation in light of the particular medical history." Further, the physician has a duty to disclose these risks to the patient. Consequently, the court held that the duty to provide informed consent belonged to the physician alone and was non-delegable, because "obtaining informed consent results directly from the duty of disclosure, which lies solely with the physician." Although the ruling is binding only in Pennsylvania, physicians in other states should note that their state may take a similar view of informed consent.

The Pennsylvania Supreme Court has taken a more conservative view of who may obtain informed consent than FDA guidelines imply. The FDA says that informed consent must be obtained by an "investigator." The agency does clarify, however, that the investigator need not be a medical doctor and that a "physician can be a subinvestigator to perform those study functions requiring the appropriate level of medical expertise." This suggests a great deal of flexibility in federal regulations and their interpretation as to who may be considered a principal investigator or a subinvestigator, and also means that an individual who is not a physician may be delegated the primary responsibility to obtain a subject's informed consent. In the context of clinical trials, this has traditionally been a study coordinator or a nurse. In Pennsylvania, *Shinal v. Toms* has restricted this view of informed consent considerably.

Failure to obtain sufficient informed consent is already the subject of many malpractice lawsuits, and the *Shinal v. Toms* ruling may provide precedent for future cases involving clinical research. A *prima facie* interpretation of the court's opinion suggests that informed consent by the physician is non-delegable. While this reading of the court's opinion is not any more onerous than a strict reading of the regulations, which potentially require that only the principal investigator perform the informed consent interview, it does place an unexpected burden on clinical research facilities. In light of the ruling in *Shinal v. Toms*, the informed consent process during clinical trials must be restructured to ensure that doctors are informing patients and obtaining consent.

This case is placing an unexpected burden on many of Pennsylvania's clinical research sites, which are putting together new procedures in order to comply with the court's opinion. Although there is evidence to suggest that medical doctors may not be the best-suited individuals to facilitate the informed consent process, it is likely to become the new normal for clinical research. Investigative teams must consider ways in which they can improve the informed consent process while working within the narrow framework established by *Shinal v. Toms*.

** Andrea Tunnard and Erin Grant contributed to this article. To read the full version (including references), visit: http://bit.ly/2BH2Gdf.*

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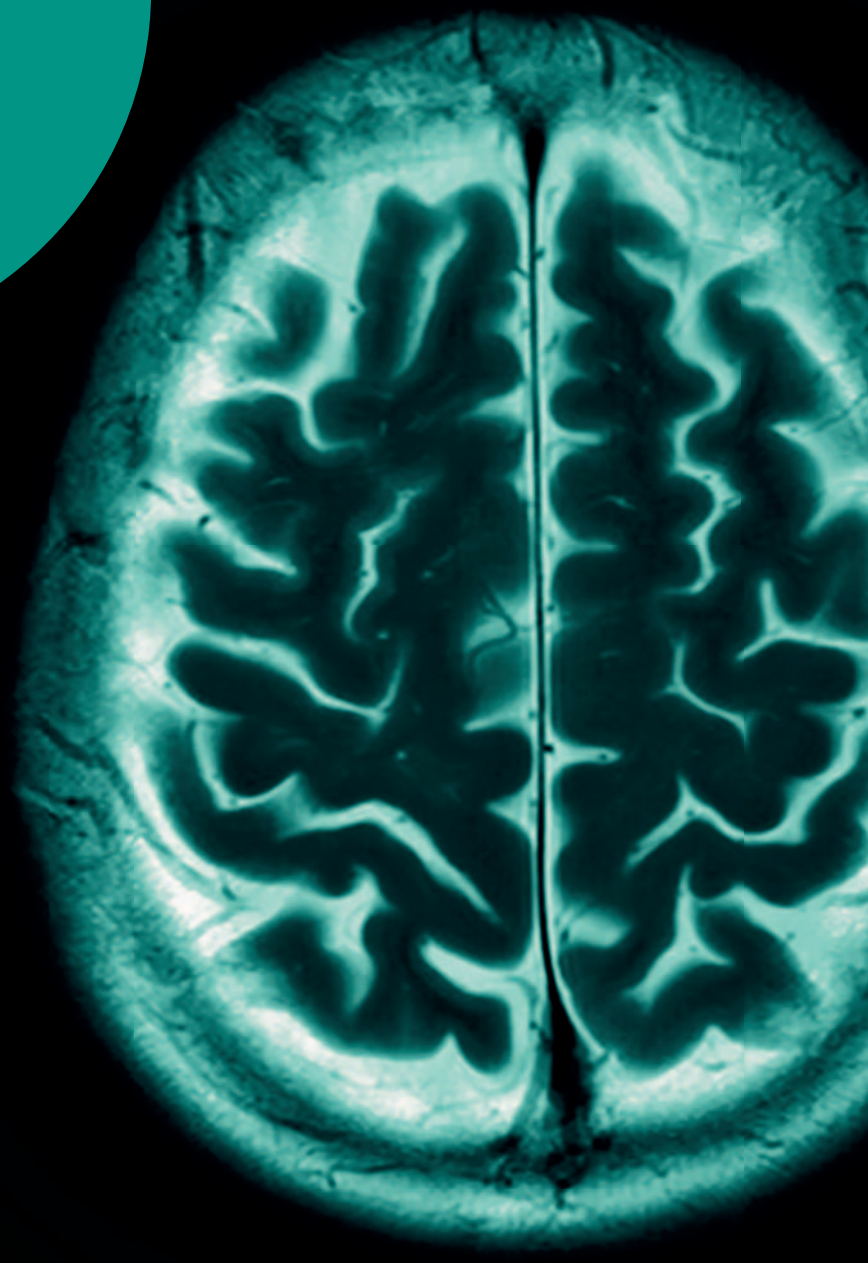

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