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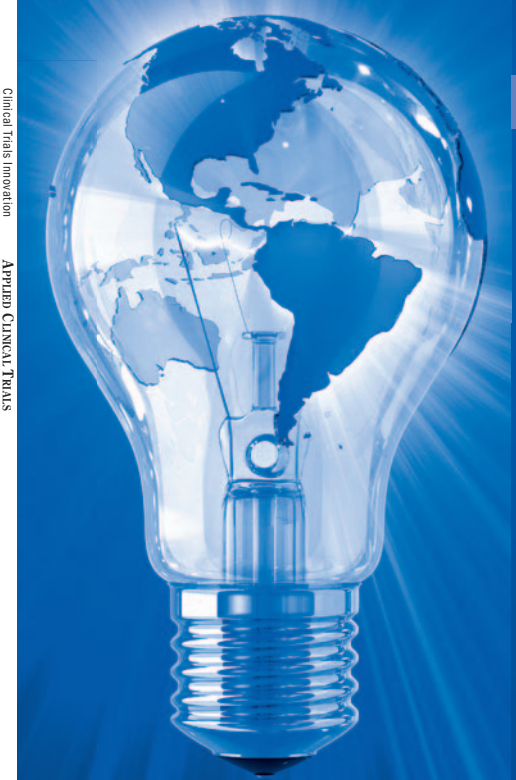

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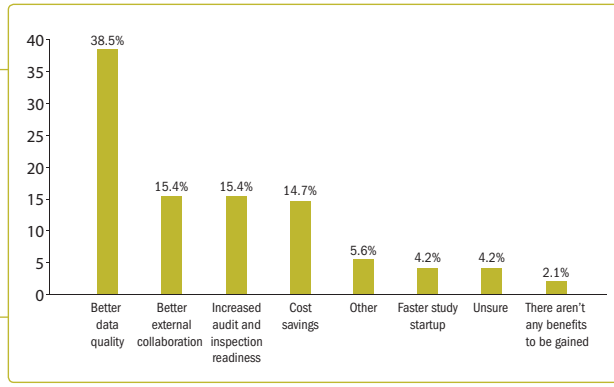

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Can EDC Be Innovative?

Innovate or die is not the crisis we face in the highly-regulated pharmaceutical industry. According to Keith Howells, Senior Vice President, Development, for OmniComm Systems, and longtime industry technology expert, the challenge is to "innovate regardless."

There are many roads to innovation, but for a technology that's been around in clinical trials since the early 2000s—and only fully adopted within the past three years—can electronic data capture (EDC) be considered innovative?

Howells told *Applied Clinical Trials* that there is a philosophical discussion: is EDC a commodity? To believe EDC is a commodity, one has to be assured that the technology offers nothing new. And if a service provider needs to create the value-add or revenue opportunities for EDC, then one business model is to build complementary products to the EDC. For example, offering solutions additional features or solutions such as clinical trial management systems (CTMS), safety, electronic patient reported outcomes, randomization, and supplies tracking.

"Our belief is that EDC is never going to be finished," stated Howells. "If you sit on it and let it go out of date, then people aren't going to want it because it's missing the new features, or it was good enough 10 years ago but the user interface isn't good enough now."

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VIEW FROM WASHINGTON

Randomized Clinical Trials Face Practical and Ethical Challenges

The high cost of conducting biomedical research in the U.S. has drawn intense scrutiny in recent years as to the efficiency of clinical trial operations, effectiveness of research oversight and the value of more flexible strategies for tapping new data sources. While the placebo-based randomized clinical trial (RCT) has long been the "gold standard" for obtaining objective, unbiased information on the safety and efficacy of medical products, the need to revise the design, performance and interpretation of clinical research to reflect changing methods and standards has drawn serious attention. Recent analyses have cast doubt on the value of highly controlled and regulated research, as seen in difficulties with patient recruitment, concerns about informed consent, and demands for more transparency in research data and results.

One sign of progress is the shift to greater reliance on a single institutional review board (IRB) to oversee multi-site clinical studies, as outlined in a recent final policy from the National Institutes of Health (NIH). The hope is that central IRBs will eliminate duplicate ethical reviews of human subject protections, an approach now common in commercial research programs.

Efforts to update the "Common Rule" governing the protection of federally funded human subject research may get a fresh start based on a June report from the National Academies of Sciences, Engineering and Medicine. A blue-ribbon panel criticizes the current effort to revise these policies, particularly a proposal for requiring informed consent on future uses of de-identified residual biospecimens.

The value of randomized trials in providing evidence on the efficacy of SSRIs and other anti-depressants is revisited in a new book by the author of the 1993 blockbuster *Listening to Prozac* amidst the continuing debate over whether these drugs are no better than placebo. Now in *Ordinarily Well: the Case for Antidepressants*, Peter Kramer examines the limitations of clinical trials, but concludes that Prozac and other similar therapies are useful despite their flaws.

Tapping real-world evidence

RCT operations and standards face further scrutiny with the approval of more breakthrough therapies based on limited clinical trial data. Sponsors also find new challenges in conducting traditional studies to test new cancer therapies, as rapid changes in standard of care often make a clinical trial outdated by the time a sponsor has gone through study design, site identification and patient enrollment.

These developments are driving efforts to augment initial research findings with more real-world evidence (RWE) found in health system and insurance claims data systems. FDA Commissioner Robert Califf says a top priority is to better leverage RWE to inform FDA decision-making, a goal also outlined in a recent report from the Bipartisan Policy Center. Pharma companies are looking more to RWE to confirm efficacy and to track safety issues and rare events following new drug approval and to support added indications for marketed therapies.

At the same time, much RWE appears highly variable and incomplete compared to RCT results, and, thus, not yet considered sufficient to document safety and efficacy for a new therapy. Even so, both regulators and researchers are looking to broader use of RWE in the future to supplement post-market research, identify novel outcomes and avoid clinical studies that could expose more patients to less efficacious treatment.

Priority to trial participants?

A tricky issue for clinical research sponsors is to decide which individuals should have priority access to drugs in limited supply, a situation that emerges related to compassionate use requests for experimental therapies and for critical marketed drugs in short supply. Continued supply disruptions for medically necessary treatments, particularly those used in emergency care and for treating cancer, often force hard decisions, particularly in caring for children with cancer where treatment routinely involves older generic injectibles often hit hard by shortages.

The research community has long recommended that participants in clinical trials should be first in line to receive a critical new therapy in order to reward their altruism and to further encourage trial enrollment. Now a task force looking to establish ethical standards for allocating scarce life-saving pediatric cancer drugs says that patients participating in clinical trials should not necessarily top the priority list.

The recommendations from the Working Group on Chemotherapy Drug Shortages in Pediatric Oncology, published in the February 2014 issue of the journal *Pediatrics* and examined further in an article published online in January by the *Journal of the National Cancer Institute*, note that such preference could smack of coercion to enter a study and also undermine their effort to base priority access on where a critical therapy is most likely to save lives and improve prognosis. An overriding goal is to avoid "bedside rationing" that leaves critical allocation decisions to conflicted physicians.

— *Jill Wechsler*

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VIEW FROM BRUSSELS

Europe Tackles New Rules for Non-Clinical to Clinical Handoff

A look at the EMA's proposed guidance revisions for first-in-human studies

Unsurprisingly, the European Medicines Agency (EMA) has decided it is time to look again at first-in-man clinical trials. As with the current European guidelines, adopted in 2007 after the disastrous U.K. trial of TGN1412, the trigger this time round is the damage done to volunteer subjects in the Phase I trial in France earlier this year.

After the death in January of one volunteer and the hospitalization of five others during a trial conducted by French research organization Biotrial for the Portuguese drugmaker Bial, French health minister Marisol Touraine called for a review of the way first-in-man clinical trials are authorized across Europe.

The reaction is similar to the furor caused by the multi-organ failure among six volunteers in the 2006 Phase I study of a CD28 superagonist antibody, TGN1412, which had been designated as an orphan medical product by the EMA the year before. That time, the product was developed by TeGenero Immuno Therapeutics, tested by Parexel and manufactured by Boehringer-Ingelheim.

Part of the reaction then was the EMA publication in 2007 of its "Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products." That is still the main advice on the data needed for appropriate design and initiation, and it is, according to the EMA, no longer up to the job. The ICH requirements—ICH M3 (R2) and the related Q&A document—are not enough either.

With this further French demonstration of the risks in progressing from the conduct of non-clinical studies to clinical trials for investigational drugs in humans, it has become clear that the rules merit reconsideration. In late July, the EMA published a concept paper on "changes intended to support best practices" (http://bit.ly/2a6aKrE), and it is seeking comments before the end of September.

So what's new in the approach? Certainly not the underlying objective, which predictably remains "to further improve strategies to identify and mitigate risks to trial participants." And not the attitude toward clinical studies, either. "Clinical trials are essential for the development of medicines and without them patients cannot gain access to new potentially life-saving medicines," the EMA prefaces its remarks.

The agency adds that the release of the concept paper is only "part of" a review of the 2007 guideline—and a slightly subsidiary one, at that. Already it has reached a view on what needs changing, based on the views of a group of EU experts, and endorsed by the Committee for Medicinal Products for Human Use (CHMP).

What the changes focus on are the parts of the current guideline that "need to be amended to take into account the evolution of practices in the conduct of these studies." Principally, it says, this is the shift over recent years to a more integrated approach, with sponsors conducting several steps of clinical development within a single trial protocol. This more structured approach, with incremental decisions on next steps based on the data collected at each previous step, makes it possible to take more account of the specificities of each drug, its mechanism of action and intended therapeutic use.

So it is time to move on from the limitations of the current guideline, which reflects practice of more than a decade ago in focusing on non-clinical aspects and the use of animal data, and which relies mainly on a single ascending dose design. Since the early years of this century, there has been a big evolution in the integration of the non-clinical data available and the pharmacokinetic, pharmacodynamic and human safety data emerging during a trial. Consequently, many studies are now performed with integrated protocols potentially combining a number of different parts, such as single and multiple ascending doses, food interaction, different age groups and early-proof-of-concept or early proof-of-principle parts. First-in-man and early phase clinical trials with multiple study parts are increasingly being submitted for regulatory review as part of a single application, the agency points out.

To cope with the increased complexity of the protocols, EMA is suggesting that there should be exploration of a dozen areas, and is seeking views accordingly. Top of the list is extending the guidance to early phase trials that include single study or integrated protocol designs.

The non-clinical aspects of the guideline also need to be expanded, the agency suggests. Provision should be made for better integration of non-clinical pharmacology and data from the toxicology testing into an overall risk assessment. New attention should be devoted to translating non-clinical data into human use by extrapolation, and the assumptions made should be verified. The minimum anticipated biological effect level approach should be more generously interpreted, taking all biological effects into account.

The role of non-clinical data should be amplified in estimating the therapeutic dose, maximum human dose level, dose escalation steps and dosing frequency and intervals. It should also play a bigger part in definition-of-stopping criteria for

the trial, and identification of safety aspects to monitor.

The clinical part of the guideline should be strengthened with new guidance on integrated trial designs and study endpoints, including decision-making aspects, and should explicitly cover more than just single ascending dose trials, incorporating other early phase trials and designs. Clarification is needed on the choice of trial subjects, on the overall dose/exposure range and scheme, including stopping rules, and there should be a rolling review of emerging human data during the study.

Once this consultation is completed and the views have been digested from stakeholders ("patients, physicians, academia, ethics committees, pharmaceutical industry, sponsors, investigators, contract research organizations and regulatory authorities"), the next stage will be further discussions among a multidisciplinary group that includes experts from CHMP and the Heads of Medicines Agencies' Clinical Trial Facilitation Group. All this will feed into a draft revised guideline before the end of this year, the EMA predicts.

No amount of regulation can hope to eliminate all risk, but with two attempts to improve the rules in less than a decade, the pressure is now on the authorities to make sure that its guidelines are at least in tune with contemporary practice. And the pressure is all the greater on the clinical trial community to make sure it gets it right with first-in-man trials.

— *Peter O'Donnell*

GLOBAL REPORT

EMA's Future Location in Doubt After Brexit Vote

The intense uncertainty surrounding the future location of the European Medicines Agency (EMA) and its 890-member staff looks set to continue for months, if not years, following the U.K.'s decision in June to leave the European Union.

According to an EMA statement in early July on the "Brexit" vote, "The implications for the seat and operations of EMA depend on the future relationship between the U.K. and the EU. This is unknown at present and, therefore, we will not engage in any speculation."

The agency acknowledged that it has already received interest from countries that are keen to host the organization in the future. EMA said it welcomes this interest, but the decision will be agreed upon by representatives of EU nations, not the agency itself.

EMA stressed that its procedures and activities would not be affected by the outcome of the referendum, and it will continue its operations as usual, in accordance with the timelines set by its rules and regulations. No country has ever decided to leave the EU, so there is no precedent for this situation, but the European regulatory framework is a very strong and flexible system that can adapt to changes without jeopardizing the quality and effectiveness of its work, the agency stated. EMA said it is in close contact with EU institutions, and as soon as concrete information becomes available, it will share it with its stakeholders.

— *Philip Ward*

CLINICAL TRIAL TECHNOLOGY

eConsent Study Provides Insights to Shape Industry Adoption

The drawbacks of today's paper-based informed consent methods for clinical trials are well understood, but the industry has yet to perfect the process and tools to best ensure human subject protection while at the same time achieving a streamlined electronic consent process.

Janssen is working to change that, releasing the findings from the company's multi-country pilot study of electronic consent technology to guide the development of industrywide practices. The eConsent study was conducted at 13 sites—10 in the U.S. and three in Hungary—in a Phase III clinical trial of INVOKANA™ (canagliflozin) in subjects with type 2 diabetes.

Each participating site received an iPad device loaded with the patient eConsent app, as well as a training app and a training webinar for site staff.

The eConsent app first informed patients that their name and all data would be time-stamped and securely stored in a database. After patients provided their approval, the app played an animated video explaining the full study and key aspects of procedures. Next came the actual informed consent e-document, along with an app-based dictionary and the ability to indicate when a word was not understood. Finally, patients took an eight-question multiple-choice quiz that highlighted key aspects of the study. Both the patient and site staff signed the document electronically, using a stylus. The study's sponsor had real-time access to all eConsent activities per patient via a web portal.

A total of 76 patients participated, each completing a detailed satisfaction survey immediately after the initial eConsent. Sites responded to a brief survey every two months and then completed a comprehensive survey after the study was completed.

Overall, satisfaction levels were extremely high from both patients and sites, indicating a broad willingness to transition to an electronic process for consent. As a whole, the eConsent functionalities and features received a "satisfactory" rating of greater than 85%. (Other possible response options were "neutral," "unsatisfied," or "not used.")

Highlights included the video (96% of patients rated it satisfactory), content review quiz (94%) and a feature that allowed patients to mark unfamiliar words (90%). Meanwhile, 77% of sites said eConsent improved the entire consent process.

Diving deeper into the survey results, here are some of the key takeaways:

Older participants adapted well to new technology. Of patients 60 or older, only 27% had experience with a tablet device. While that could prompt cause for concern, older users universally reported high satisfaction on each eConsent feature. As a whole, all age groups rated the process "easy" or "very easy" to use and no one with experience using paper forms said they thought the traditional process was better.

More time to focus on what's important. When site staff were asked about the length of time it takes to use eConsent versus paper forms, 46% reported it was about the same. Twenty-three percent said it was faster, and 23% said it was more time-consuming. Sites could more quickly address items patients didn't understand or missed on the form—which didn't always result in a workload reduction, but was certainly a process enhancement.

Improved patient understanding and engagement seen. Most (69%) of the sites reported eConsent as a helpful tool for improving subjects' engagement during the consenting process and in boosting their initial understanding of material (also a key advantage reported by patients). In addition, 38% of sites said that eConsent improved patients' desire to enroll or stay in the trial.

Valuable insights into the patient's mind. The sites and sponsor were able to see which app features the patients used and how much time was spent on each section, as well as which words were marked as unfamiliar or looked up in the dictionary. This feedback is a promising feature as the industry seeks to make clinical trials easier for patients to understand.

Plan for local differences. All of the app's content must be translated into native languages. In addition, country-specific requirements will have to be incorporated. For example, Hungary requires patients to provide date of birth and place of birth.

Janssen is sharing these and other findings while leading TransCelerate's eConsent work stream. In parallel, Janssen is preparing a new eConsent study with visually impaired patients in the U.S. and Canada. The 15-site study will include five different consent forms and additional audiovisual features. Three more studies will kick off within the next year to broaden the global perspective and assess other eConsent functionalities and patient populations.

The benefits of eConsent are clear, but now it's up to the industry's many players to come together to share their learnings and remove barriers to implementation. This also requires close collaboration with patients, trial sites, health authorities and ethics committees.

As with many new digital technologies for clinical trials, eConsent is a tool to enhance the site-patient relationship, not replace it. A positive experience at the onset of a trial is a gateway to better engagement throughout the study and afterwards, bringing our industry closer to patients—our most important allies.

— *Hilde Vanaken, Ph.D., is director of the R&D Operations Innovation Department at Janssen Research & Development and is the Transcelerate eConsent Workstream Leader*

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An Executive Summary

Investing in Today's CRA Talent to Ensure a Stronger Tomorrow

The importance of Clinical Research Associate training to support effective trials

By Monique Heiser Wong, Senior Manager, Clinical Development Services, Covance Inc

The clinical trial landscape is witnessing an increase in Phase III trials that average more than 3,500 patients. As more of these large trials continue to emerge, many contract research organizations (CROs) and sponsors are struggling to recruit qualified clinical research associates (CRAs) to support the influx of work.

Lack of experienced talent represents one of the main challenges facing the market, impacting sponsors and CROs alike with increased costs and extended timelines. Yet the urgent need for qualified CRAs will continue given that the demand in the field is projected to grow by 36.4% from 2012 to 2022 in the US, an issue also reflected worldwide.

Examining Recruitment Barriers

The clinical trial industry is acutely aware of the pressures. To stay abreast of this urgent situation, as noted in the Association of Clinical Research Professionals (ACRP) position paper, A New Approach to Developing the CRA Workforce, the industry needs to assess current standard operating procedures (SOPs) and examine barriers blocking new talent from filling positions.

At Covance, we followed this guidance and brought together our leaders to holistically assess the market and our current investments. We found the industry truly lacked a harmonized global training program to develop CRAs—early in their careers—creating a major hurdle for job seekers. Furthermore, many scam training programs offer dubious certifications to CRA candidates interested in building skills within the field.

Proactively Growing the Talent Pool

Recognizing this gap in training, we developed a global program to attract and retain talented people: the Covance Monitoring Excellence Academy (MEA). We wanted to give candidates from around the world the opportunity to grow into the CRA role, which ultimately enriches our lifeblood for the good of patients and transforms how we manage clinical trials.

The academy is more than a simple training program. MEA establishes an accelerated path through tailored scientific courses, interactive modules, hands-on experience and an ongoing mentoring program. Trainees receive a solid foundation that lays the groundwork for a rewarding career path.

Building the Pathway to Success

The Covance Monitoring Excellence Academy is designed with two pathways to hire staff and train them in a standardized global fashion. The first path focuses on what we call the CRA "Assistant Role." These candidates have the relevant education but limited experience in a clinical research setting. With guidance from experienced team members, they can work at in-house roles and learn all the aspects of being a CRA, creating the perfect opportunity for recent graduates looking for a fast tracked career path as a CRA.

Industry experienced staff, such as research nurses, site study coordinators or clinical research coordinators are ideal for the second path. Here, the MEA courses teach them how to effectively manage sites in clinical trials as a CRA. In many cases, these staff are remote employees, working from their home offices while in the MEA program.

Regardless of the pathway, we've found that trained staff feels empowered to bring a more consistent approach to how they monitor and manage sites, reinforcing our drive for quality, accuracy and excellence. And, the CRA team, having diverse backgrounds with varied experience levels, offers a more innovative, holistic and unique perspective, using a "critical eye" to judiciously manage our trials—a true value to everyone.

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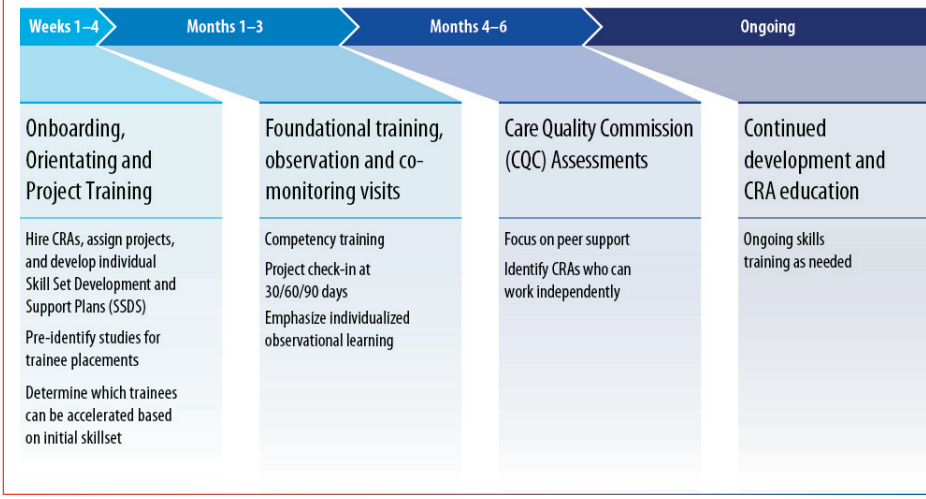
A Flexible Curriculum, Focused on Growth

The MEA program offers tailored tracks based on a candidate's individual level of industry knowledge and experience. Over a three- to six-month period, participants advance their clinical operation competencies through a comprehensive blended face-to-face and web-based curriculum:

Regional Training Modules	Allows candidates to participate in training modules based on experience in the industry—ranging from team roles and responsibilities to clinical trial design to remote monitoring
Clinical Foundations	Provides an overview of activities, processes and components of a clinical trial, emphasizing the roles and responsibilities of the sponsor, sites, ethics committees and the CRA
Peer Support and Observational Training	Offers participants the opportunity to partner with and observe skilled CRAs to further develop competencies, expand critical thinking skills and gain co-monitoring experience
Regional Case Studies, as applicable	Encourages learning via scenario-based training case studies created from corrective and preventive actions (CAPAs) and examples from Clinical Quality Control (CQC) visit findings

The monitoring excellence academy onboarding timeline



Supporting Employees, Clients and Trials

Through the MEA program, graduates gain comprehensive real-world experience and a thorough understanding of GCP and ICH regulatory requirements all while working in a supportive network of skilled and trained CRAs.

Participants work with a regional point person that provides real-time support when questions arise and ensures the individuals understand all aspects of the clinical trial monitoring through the MEA program period and beyond—before accepting any individual assignments. This process ensures the highest data quality for more successful site performance.

"Clients have always chosen to work with Covance because of our experience, our reputation for quality and our therapeutic area expertise across the entire development spectrum, from nonclinical through Phase IV and safety monitoring," said Dr. Rob Davie, Vice President and General Manager for Global Phase II-IV, Clinical Development.

"Our clients' main priorities are data integrity and patient safety and our CRAs are the first line of defense in delivering. These talented and driven CRAs are one of our great assets and we work hard to reward their efforts from the moment they walk in the door at Covance—whether they join us through the CRA Monitoring Excellence Academy or via the traditional experience-based road." Site staff and clients deserve to partner with supported dedicated research professionals who are knowledgeable about the science of monitoring and its collaborative nature.

Investing in the future of talent through the Covance Monitoring Excellence Academy is important for the future of clinical research. These individuals are the innovators of tomorrow who are ready to make a difference today. We continue to hear from our clients on how satisfied they are with the collaborative coursework and the services of their new enthusiastic CRAs. If you'd like to learn more about Covance's extensive clinical offering or the Monitoring Excellence Academy opportunity, **please visit our website: http://careers.covance.com/CovanceCRA.html**

"The MEA gave me the necessary training that helped me make the jump from study coordinator to CRA. I feel that I have the right tools to excel in my role as a new CRA with continuing support from my trainers, mentors and other CRAs from the program."

-Recent MEA graduate

PATIENT ENGAGEMENT

Patient Centricity: From Concept to Reality

A patient-centric approach to a Phase IV trial for an MS treatment resulted in lessons that can be applied to future therapeutic studies for this and other rare diseases.

The concept of patient-centricity in clinical trials is not new, and it is gaining traction among sponsors and investigators. However, this term has taken on a broad, often vague, meaning. Implementation of patient-centric strategies can be complicated and often lacking in measured results. The concept brings up a wide range of questions: what patient-centric strategies are the most effective? When and how should patients be engaged? How does a study sponsor gain consensus on new approaches for study design and patient recruitment? What is the impact of a patient-centric approach on study milestones and outcome?

Lesley Schofield, Head, Medical Affairs Clinical Operations, Medical Affairs & Registry Trials, Novartis, and Nancy Mulligan, Senior Operations Director, Patient & Physician Services, United BioSource Corporation (UBC), implemented patient-centric strategies while partnering on Novartis's PREFERMS study. The study looked at patient retention of the study drug vs. currently approved disease-modifying therapy in patients with relapsing-remitting multiple sclerosis (MS).

In the following Q&A, Schofield and Mulligan share their patient-centric approach, which included ensuring the PREFERMS study engaged MS patients in key study design decisions, achieving recruitment goals by recognizing patients' strong involvement in the MS community, and customizing site services to best support investigators and their healthcare teams.

Lesley Schofield | Nancy Mulligan

Q: *This study exceeded enrollment projections, correct? What strategies were most impactful to achieving that?*

SCHOFIELD: We enrolled 881 patients across 130 study sites in the U.S. There were a number of challenges to reaching this milestone—competing studies, fatigue among study sites and the protocol's data collection schedule, to name a few. From the start, we worked closely with sites. We listened to their feedback on the challenges to protocol implementation, and ultimately there was an amendment based on their feedback that helped boost enrollment. We knew that to succeed, we had to minimize the burden on the site, and on the patient.

MULLIGAN: Our UBC team had a staff person working individually with each study site. The recruitment specialist talked to study coordinators on a weekly basis, to evaluate tactics that were in place and provide insights on anything else that could be done to reach patients. We implemented a mix of tactics that would be most effective for each site. Recruitment tactics included mailings, advertising, online presence and participation in community events. We launched a grassroots strategy to reach patients in their own backyard. We found that participating in MS walks and runs was critical. Site personnel would host a table or booth with study information or participate in the walk/run as a team. These events not only raised awareness and credibility in the community, they also helped to keep the study teams motivated and engaged.

Q: *The MS community is known to be highly motivated and highly involved. Patients have formed strong support networks, rely heavily on the Internet for research, use social media and participate in online communities. How did you tap into this community for the* PREFERMS *study?*

SCHOFIELD: This study initiated in 2012, and we knew that it was crucial to reach people with MS online. One approach we took was PatientsLikeMe, an online community of people with different health conditions.

Through PatientsLikeMe, we were able to inform people about the study, reaching members who expressed interest in MS research. To extend our online presence, we created a Facebook page for the study and posted IRB-approved content and advertising on Facebook. It was exciting to see the several thousand "likes" that accrued over the course of the study. We also used online advertising to drive traffic to the study website, which featured an online screener, making it easy for visitors to see whether or not they may qualify for the study.

Q: *Study sponsors are increasingly looking to collaborate with patient advocates. How did this occur on the* PREFERMS *study?*

MULLIGAN: Patient advocates can bring a lot to a study, but it's important to remember that your study is not their number one priority. Their priority is to get the best possible healthcare and services for the members they support. If your study can fit those objectives, then you will get access to incredible infor-

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Presenter:

Bernadette Tosti
Senior Director of Patient Recruitment, Site and Patient Networks, Quintiles

Moderator:

Lisa Henderson
Editorial Director, Applied Clinical Trials

As of March 2016, 11% of research sites industry-wide fail to enroll a single patient and 37% of sites under-enroll, creating inefficiency and lost productivity. We need to significantly improve to involve fewer sites and engage only the best leaders in each therapeutic area, reduce travel and administrative costs, and align process for easy start-up.

Quintiles is 1) pioneering early planning, 2) forming new and innovative relationships with industry partners, 3) developing strategic alliances with the right research partners, 4) using new technology and communication tools, and 5) creating effective physician networks — all to place more focus on patient and site engagement.

Key Take-Aways:

- Ways that pre-planning drives patient engagement.
- Using patient and investigator insights can yield extremely valuable results.
- Engaging advocacy groups ensures a robust support model for patients.
- Communication, technology, and innovative services play a part in transforming clinical development, especially patient recruitment.

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mation that will make your study more relevant and successful.

As Lesley pointed out, PatientsLikeMe was critical to our ability to reach MS patients. Thanks to that organization, we had access to 33,000 patients we could reach out to for feedback on language and messaging, as well as potential participants.

We also observed and participated in online conversations, including patient blog sites and community groups. This enabled us to get an insider's view of what patients are experiencing, what information they're looking for, and what they need to live with their disease, because this truly is a disease patients live with for many, many years.

Q: *The* PREFERMS *study was among the first of Novartis's studies to utilize a Facebook page. Were there internal roadblocks to that launch? How did you overcome them?*

SCHOFIELD: Whenever you aim to try something new or establish a new paradigm, there are pain points. To gain internal consensus for new recruitment methods, we had to be thorough in our recommendation—explain what we wanted to do, how it would work, and the messages that would be communicated. As with any communication, it was important to listen. To address and alleviate concerns. In this case, for example, we provided detailed information about how the Facebook page would work, and talked through the nature of the online posts, and how that would be managed. The internal review for the study Facebook page took several months and several modifications and repeated attempts before it was approved.

Q: *Technology and social media enable sponsors to better engage patients in studies.* How *was this part of the recruitment strategy for* PREFERMS?

MULLIGAN: We know that most MS patients first begin to have symptoms between the ages of 20 and 50, so it's a young, tech-savvy patient population. As I mentioned, we launched an online screener on the study website so patients could easily learn more about the inclusion/exclusion process. We leveraged the Facebook page that Novartis set up and were able to reach patients through that channel. We utilized geotargeted ads to reach patients living near specific study sites, and since we know that MS affects significantly more women than men, we tailored our online advertising to that segment of the population. We also advertised the study on Craigslist, a free listing that generated referrals.

Q: *With the increased focus on patient-centric tactics, why was it especially important to take a patient-centric approach with this study population?*

MULLIGAN: MS patients have formed a strong community, and they're willing to share a lot of information about their disease, treatment successes, and challenges. MS patients are incredibly educated about the disease, and they're really leading the way in how future studies should be conducted. They're directing the show in a positive way. They do a ton of research and learn from one another.

Patients want to learn everything they can so they know what they'll have to live with—what they may be up against. MS patients often know about studies and treatments in development before their healthcare professionals. They know about drug availability and what side effects other patients may be experiencing.

As recruitment specialists, we really have to do our homework and become experts in every therapeutic area that we work in; for MS it's almost like teaching a computer class to a group of information technology experts. It makes recruitment easier in the sense that patients already understand a lot about the study process, but harder in the sense that they may only be interested in very specific treatment options.

Q: *In addition to the* PREFERMS *study, how are you working with sponsors to gain patient insight on study design and enrollment?*

MULLIGAN: I always advise sponsors that collaboration early in the study process is essential. I can't emphasize enough the value of gathering insights from a variety of stakeholders—whether that's the patient community, prescribers, KOLs—and making study design decisions based on their feedback.

My team conducts in-depth interviews and focus groups to gather patient input. We're able to learn about potential challenges to study participation. Qualitative research can help a sponsor understand which study requirements may be too burdensome on a patient. Is the visit schedule taxing? Are the patient reported outcomes tools suitable to the patient population?

Early patient involvement, whether through surveys, focus groups or advisory boards, is the best way to get good information that will set you up for success.

Q: *Gaining consensus for new, patient-directed strategies often requires significant time and effort.* You *paved the way with this study.* Do *you see a shift in the practice of being patient-centric with research?*

SCHOFIELD: We're making a significant push to ensure we're putting patients first. To really be patient-centric, we need to move beyond the buzzword. To take steps to try to understand the patient experience, whether in a clinical study or in day-to-day living with a condition.

In the PREFERMS study, we successfully implemented a combination of patient-centric approaches. We involved the patient early and often in the process, not just in the beginning when we developed the protocol. As we reached out to various channels and expanded our recruitment strategies, input from patients helped us find the right participants. The PREFERMS study completed enrollment two weeks ahead of schedule. The study has concluded and results are being analyzed. Through the drug discovery process we seek to innovate. That refers to the science, yes, but can't we also seek to improve the patient experience in that process?

— *Lesley Schofield and Nancy Mulligan*

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Front & Center

Turning Signals Into Action:
A New Model for Risk-Based Monitoring

A new solution will seamlessly and electronically exchange data from the RBM system to the EDC platform, and vice versa.

In this interview, Jeff Beeler, Vice President of Product Innovation at Merge, an IBM company (eClinical Division), discusses risk-based monitoring (RBM) and how the company is innovating a 25-year-old manual process to enable better monitoring decisions.

What do you think is driving the shift toward risk-based monitoring?

Actually there are several things driving this shift. Recently, regulatory compliance from ICH E6(R2) addendum was released. The FDA and EMA have now both produced guidance for RBM. Industry working group TransCelerate BioPharma and CTTI, which is the Clinical Trials Transformation Initiative, have also been heavily involved in this space.

Quite honestly, it's a better way of doing trials and what we're looking for out of RBM is better data quality, enhanced patient safety and, potentially, cost savings.

Are companies adopting RBM and taking advantage of its potential?

It's actually been a very slow process and, in some cases, it's even nonexistent. There are certain segments—specifically large pharma and groups that participate in TransCelerate— that are evaluating methods and sometimes creating their own methods. As we get closer to the ICH guideline adoption, this trend will filter to the middle and smaller size companies.

Jeff Beeler
VP of Product Innovation
Merge, an IBM Company — eClinical division

The technology market is responding to this. Our partnership with Remarque Systems enables the use of machine learning to automate source data verification (SDV) strategies and help our customers make better monitoring decisions. Remarque has trademarked this functionality: Signal Driven SDV™. We have integrated our systems so that data flows out of eClinicalOS (eCOS), which is the Merge EDC platform and into Remarque, which is the RBM system. It looks like one system and it acts like one system from an end-user point of view. However, this data seamlessly exchanges hands. The data exchange is going to actually increase the responsibility of the sites to get data into the EDC platform. It's going to produce greater data accuracy because the EDC system and Remarque RBM Systems are looking at the data on an ongoing real-time basis.

Can you describe your company's new framework for RBM? How is it different from what is currently on the market?

We want our process to be more efficient and available for companies of all sizes, regardless of what phase the trial is in.

Central to our RBM approach is the elimination of manual processes, which we do in a number of ways. We want to help reduce pre-visit preparation time by reducing or eliminating phone calls, emails, and spreadsheets going back and forth. Also, we can reduce time on-site and post-visit follow-up by lessening time spent completing monitoring reports.

Our solution will allow the CRA to go back and review specifically what they did by referencing the audit trail that's held within the EDC system. This solution brings structure, consistency and traceability to an otherwise fluid process.

This is a process that's been exactly the same for the past 20 to 25 years. People go out, they monitor data, they send CRAs out with information that comes from the data management group, they query data, and they look at 100% of the data points that are captured within a clinical trial. So, every single piece of data that's entered into the trial is reviewed for accuracy and to determine if it's been transcribed from the case report form to the EDC system correctly.

That's really a big problem because there are hundreds and even thousands of data points. But some don't have a great deal of meaning or depth within the trial.

Our solution pulls out the key risk

indicators and sets it up so that the monitors go out with a specific plan. They can look at the data as a holistic measure of their site compared to data at other sites so that they can find things like fraud, which can be indicated by a digit preference. For example, if someone is fabricating data, they may be entering zeroes as the last digit of every single number that they enter. That's something that RBM can help find.

What we're doing with this solution is transforming way data are being monitored on an ongoing basis. Let's look at the definition of risk in trials. It's not risk of getting caught for doing something wrong; it's not risk of finding a piece of data that's wrong. It's risk in terms of your overall trial and being able to assure that you have completely captured your data as accurately as possible. And the key risk indicators can be anything from adverse events to an efficacy endpoint.

Another example, if a site is over- or under-reporting data in terms of adverse events, you don't want that site to change the actual number of adverse events that are reported for a study just because they're over-reporting and conversely, you don't want them to under-report the adverse events.

So things that the monitor used to do with spreadsheets attached in emails, and a phone call from a central monitor, now will be exchanged electronically from the RBM system into the EDC system. The data exchange will actually increase the responsibility of the sites to get data into the EDC platform immediately.

How can the small- to midsize organizations with fewer resources keep up?

All organizations, regardless of size, can leverage this technology and benefit from finding risks in real-time. Potential problems can be addressed, mitigated, or all together avoided by leveraging machine learning to address the issues.

All organizations, regardless of size, can leverage this technology and benefit from finding risks in real-time. Potential problems can be mitigated or avoided altogether by harnessing the power of machine learning.

For example, many systems can produce beautiful charts, graphs and other analytics in hindsight. However, we are actually able to make recommendations in real time. Smaller organizations will benefit by focusing their resources and time on signal-driven issues with a clear idea of what issues are actually being discovered.

The eClinical division of Merge Healthcare, an IBM Company, is a leading provider of cloud-based software solutions for the clinical research industry. Our flagship products include eClinicalOS (eCOS) and CTMS for Investigators (CTMSi). For more information, visit eclinicalos.com.

Our solution helps the small- and mid-sized organizations, like CROs and sponsors, achieve a higher level of data sophistication without a larger pool of resources.

When is the ideal time to implement the approach you're describing? Do companies need to wait until they're ready to start a new trial?

Unlike other RBM solutions, our approach can be implemented at any time while the trial is running. That is important because, in my experience, most trials are behind budget due to data review and monitoring from the outset.

This approach bridges that gap and allows operations teams to quickly, efficiently and safely review data to make those complex monitoring visit decisions. In turn, it reduces the risk without compromising patient safety.

With the new ICH guidance expected to be announced later this year, can you describe how it will affect clinical operations overall? Can the RBM method you're working on help with compliance with these guidelines?

Most of the RBM systems currently in use are business intelligence tools, with charts, graphs, dashboards and so on. But what if the central monitor or data manager doesn't know what to do with this data? What if it doesn't make sense? We give the monitor or the data manager information from the RBM system that instructs them what to do with the data: Query this site for this reason. Look at this subject and query this data point. This is what sets our system apart from others in the industry.

The beauty of it is now that all of the data are in one place with one audit trail; we can actually do forensic monitoring. You can determine that yes, the monitor was on site, yes, the monitor did take this action, and yes, the monitor did take this amount of time to review the data. And that is extremely important in order to operate within the ICH guidelines.

PATIENT RECRUITMENT

Innovations in Patient Matching

Two years ago, *Applied Clinical Trials* looked at the technologies intending to close the ever-elusive patient recruitment gap (see http://bit.ly/2auxSRm). In that time, other innovative approaches have emerged, four of which are briefly detailed below.

Patient iP. Patient iP is a platform that securely de-identifies and aggregates electronic health record (EHR) data so that clinical trial protocols can be automatically processed to more quickly identify where and how many patients match the inclusion/exclusion criteria requirements. Michael J. Margiotta, CEO, told *Applied Clinical Trials*, "EMRs are just a repository of patient data. Those systems don't capture data in a way that can be aggregated or analyzed and perform data mining on the patient populations." This is where Margiotta stepped in—to provide a platform that would be able to leverage EMR data in a way the software currently can't. In 2014, he launched his company to be able to match patients to specific criteria based on aggregated information including genetic markers, blood values, medications, and more to find those exact patients very quickly. Think of it as an EMR booster.

For contract research organizations (CROs) and sponsors, they can use Patient iP for protocol modeling—making sure patients actually exist for the protocol they have designed; as well as site feasibility. Sites can quickly know how many patients in their networks are potential participants through the EHR. Or for practices considering clinical research, they can find out how many patients in their practice are eligible for a current protocol.

ePatientfinder. Tom Dorsett, CEO, believes that though many solutions for patient recruitment in clinical trials have emerged, there exists a lack of actionable models for getting those patients into clinical trials. And here is where his solution comes in. ePatientfinder uses a three-tier funnel or level of screening to find the highest quality referrals. The funnel includes ePatientfinder sending potential trials with patients to a physician through the EHR. If the physician opts in, ePatientFinder reaches out to patients initially to see if they are interested, then provides an IVR pre-screen survey to uncover any subjective issues that may not be in an EHR. Those patients are then referred to the opted-in physician for a consultation.

According to Dorsett, the platform builds on the trust inherently found between patient and doctor, and is a process that keeps the physician in the drivers' seat, which Dorsett says they appreciate. In addition, the company has been achieving the best quality referrals to sites, and has feedback from the sites themselves that the three-tier screening provides very high conversion rates.

MM LAB. In March 2016, MolecularMatch, a cloud-based, clinical informatics company that works with labs, hospitals, genomic cores and physicians to connect cancer patients to treatment options, launched its MM LAB software for pathology labs and others to match patients' test results to personalized cancer treatments, including clinical trials and experimental drugs.

MolecularMatch offers a public-facing website for people looking for oncology treatments, searchable by diagnosis, specific gene mutation, comorbidities and more. The data behind the search is culled from web-based information sources including ClinicalTrials.gov, registries, institutions, PubMed abstracts, COSMIC and more. It is fully automated to create structured data from unstructured sources.

According to Xuan Shirley Li, PhD, Chief Scientific Officer of Molecular Match, the MM LAB software was a natural next step for the company's offerings. MM LAB generates a customized report from its culled data of specific trials and treatments, based on the specific markers that come from tumor testing. Basically, for labs, the software can be used to generate a value-add service for those physicians or health networks.

Quintiles. The company's precision enrollment model, which is comprised of a network of 100 U.S.-based oncology centers, is designed to accelerate patient recruitment using pre-identified patients based on study and biomarker criteria, across broad geographic areas, and incorporating EHRs and other data sources. In this newly-launched model, patients, upon entering the network, have their tumors tested. The genomic analysis and alterations of these tumors are reported back to the patient and site and can be matched to protocols using the genomic alteration criteria for the protocol. It isn't until a qualified patient is identified that the site is activated.

In this article, http://bit.ly/2asGcV2, Jeff Ventimiglia, Director, Site & Patient Networks, Quintiles, explains that study start-up time is reduced because the site previously joins the Quintiles network and fills out all the documentation and service agreements and joins the Quintiles Infosario Site Gateway. A site is activated once the patient is identified and the remaining start-up activities take 21 days.

Also, a recent pilot conducted by Quintiles suggests potential to increase screening rates and shorten timelines for clinical trials by providing a broad genomic panel rather than using a single biomarker.

Read the full version of this article at http://bit.ly/2aMXpVl

— *Lisa Henderson*

DATA ANALYSIS

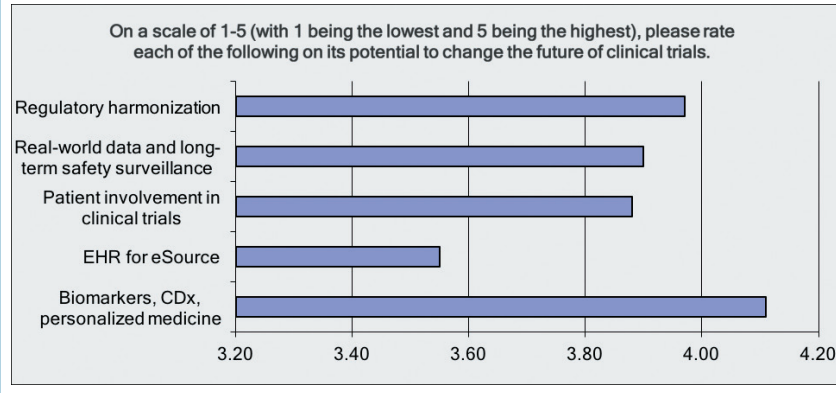
The Pluses and Minuses of Innovation

There is hype. And there is innovation. There are expectations and reality. While the chart at right is from our latest survey conducted with SCORR Marketing on innovation, this question itself doesn't use the "i" word. Something that has the "potential to change the future of clinical trials" should be considered an innovation, but of the five choices we gave, which is a true innovation? And does it matter if it indeed changes the future?

The survey delved much deeper into what respondents think about innovation, what types of innovation is or is not being implemented, and how innovation is viewed by stakeholders. These results can be downloaded at http://bit.ly/2ah8gIp.

The survey also found that the majority of respondents feel that CROs are most accepting of innovative processes, while sites are not; an equal number of companies have or don't have an innovations department or infrastructure (43.4%); and the most often cited reason for hindering adoption of technological advances is cost. —*Lisa Henderson*

Contenders or Pretenders?



Source: *Applied Clinical Trials*, SCORR Marketing Survey, June 2016

To see more Clinical Trial Insights articles, visit
appliedclinicaltrialsonline.com

Insights Into Capturing Collaborative Value

Research reveals a need for sponsors to be much more consistent, disciplined and focused in their CRO usage

The fastest growing area of R&D spending is outsourcing. By 2017, the Tufts Center for the Study of Drug Development (Tufts CSDD) estimates that contract research services will overtake all other areas as the largest category of R&D spending. Pharmaceutical and biotechnology company reliance on outsourcing is high and increasing as companies continue to seek lower fixed cost operating models while leveraging externally-sourced global capacity and expertise.

Despite the new and evolving outsourcing models that sponsor companies have implemented over the past two decades—from transactional to functional service provider and integrated alliances—drug development operating performance has not improved. Overall, clinical trial failure rates are higher than they were in the mid-1990s; development cycle times are longer; patient recruitment and retention rates are lower; and drug development costs have continued to escalate.

Anecdotally, sponsor and contract research organization (CRO) executives frequently point to the lack of trust and insufficient communication as the major factors challenging sponsor-CRO collaborative effectiveness. Recent research conducted by Tufts CSDD suggests that there are more tangible and practical executional areas contributing to inefficiencies and ineffectiveness.

The research results suggest that pharmaceutical companies aren't fully invested in their external collaborations and that CROs remain vendors, not partners. Outsourcing practices implemented by sponsor companies lack discipline and ultimately compromise the ability of more integrated, multi-functional alliances to deliver on their objectives and promises. Sponsors inconsistently use a variety of approaches and models that produce internal friction and uncertainty.

Practical insights from Tufts CSDD research highlight two core areas that would better leverage sponsor-CRO collaborations: Accommodation of CRO input into development planning and protocol design; and more consistent and disciplined implementation of collaborative relationships.

Giving CROs a voice in planning

In past studies, Tufts CSDD found that more than 80% of CRO companies report that sponsors rarely, if ever, accommodate CRO suggestions to improve protocol design executional feasibility. CROs also report that key measures to monitor and reward their performance are intimately tied to the executional variables dictated by protocol design.

Kenneth A. Getz
MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCRP, both in Boston, MA, e-mail: kenneth.getz@tufts.edu

The most frequent key indicators used by sponsors to evaluate CRO performance include enrollment speed (34% of sponsor companies), data quality (27%), study start-up speed (18%) and the number of change orders (14%)—all areas that are highly associated with protocol design. And research has shown that protocol complexity is associated with a higher number of amendments; unplanned, unbudgeted and disruptive changes.

Given the collective expertise of study teams comprised of internal and external members, early collective engagement related to planning and study design would contribute to a shared vision, better alignment of effort and incentive around performance goals and more operationally feasible protocols.

More consistent and disciplined execution

Despite the best efforts that go into conceptualizing and structuring outsourcing relationships—steps typically handled by more senior management—during execution these relationships underperform. Past and current Tufts CSDD studies show that in all but rare instances typically involving very small sponsor companies, no CRO partnership is used in the way it was intended.

Sponsor companies use a variety of conflicting outsourcing models to support their studies, mixing and matching the use of internal staff with niche and full-service providers under various relationship arrangements simultaneously. In many instances, sponsor companies vary the types of outsourcing relationship models used on a study-by-study basis.

There is a complete lack of standardization about how outsourcing strategy is defined, understood and enforced within organizations. Some strategic partners receive less work

than do non-partner CROs. Project teams often give non-partner service providers work that already has been contractually promised to alliance partners.

Although there are situations where these approaches may have been justified, most often they reflect reactive or project-specific choices made without awareness for, or regard to, the company's overall outsourcing strategy and tactical intent.

Sponsor companies report that they have difficulty standardizing and enforcing consistent outsourcing approaches for a variety of reasons. Many companies are simply too large and too fragmented. Many clinical teams do not even know what outsourcing relationships are being used to support active and recently completed studies.

Legacy activity underway when new partnerships form also contributes to the problem. Clinical teams typically have established their own relationships with select service providers and resist handing-over existing projects to new partners.

Companies going through mergers and acquisitions, in particular, often find themselves forced to allow inconsistent practices across organizational functions to ensure that legacy projects are completed as new approaches are introduced.

Another dynamic that contributes to the inconsistent use of multiple sourcing models is turnover of key senior staff championing, overseeing and implementing collaboration strategies. Partnerships that have not sufficiently been adopted are prone to fall apart when new executives, who might have different ideas about sourcing models, take charge. And many large sponsor companies that have formed strategic outsourcing relationships still have significant in-house development resources creating internal competition with comparable external resources.

Inconsistent and undisciplined approaches are the enemy of efficiency. They introduce incremental direct and indirect costs required to support customized approaches. In addition, collaborative practice experience and efficiencies are isolated to individual studies and don't scale across the development portfolio.

Maximizing collaborative value

Sponsor companies must fundamentally change their outsourcing execution to capture a higher proportion of expected collaborative value. Introspective assessment of current practices will play an important part in identifying opportunities to drive more consistent outsourcing execution. In-depth, open discussions with CRO partners will be equally revealing. Two frameworks may also help drive more consistent, disciplined and focused CRO usage.

> **Inconsistent and undisciplined approaches are the enemy of efficiency. They introduce incremental direct and indirect costs required to support customized approaches.**

The adoption of adaptive designs helps facilitate a shared line of sight into development planning and study design. Adaptive trial designs offer internal teams supplemented by external staff the ability to shape and anticipate study design changes through scenario planning and trial simulation prior to finalizing the protocol. Rigorous upfront planning will force partnerships to collectively challenge protocol feasibility at the right time.

A second framework, patient engagement, holds promise in changing the CRO-sponsor relationship in a variety of ways, including shared interactions with patient advocacy groups, healthcare providers and payers to shape development planning; soliciting patient feedback into protocol design feasibility; improving study volunteer access and convenience (e.g., study volunteer assistance services; telemedicine; home care and mobile nursing networks; interactive and wearable technologies); disclosing lay-language clinical trial results; and performing robust analysis of patient health information and real-world observational data pre- and post-drug product approval.

Sponsor companies are piloting and adopting a variety of patient-centric initiatives. Industry consortia—most notably TransCelerate Biopharma Inc.—are also focusing on new approaches to support patient engagement and clinical study operating efficiency. Many CROs are looking to proactively innovate under a patient-centric operating environment. All of these initiatives must be well coordinated across the clinical research enterprise if they are to produce the desired impact on drug development efficiency and performance.

There is much practical and actionable work to be done to better leverage the value of collaborations. Tufts CSDD research reveals two major opportunity areas that may yield an immediate positive impact: systematically engaging CRO partners to participate in planning and study design; and consistently implementing outsourcing strategy and tactics across the portfolio.

Given the current global drug development operating environment, where performance as measured by success rates, cycle time and cost is not improving, it is essential that sponsors and CROs capture more potential collaborative value.

The Data-Decision Debate: To Share or Not to Share?

Claire Sears, PhD, Elisa Cascade, Tammy Klein

Exploring the benefits from cross-company data sharing for study planning and investigator selection.

We all know that finding the right investigative sites to conduct clinical trials is a critical step in ensuring the success of a study, and this task can be particularly complex in large global studies. When you consider that costs associated with initiating a site are estimated at $30,000, but 10% to 20% of investigative sites fail to enroll a single patient and an additional 37% of sites under enroll,[1] it is no wonder that R&D costs are so high. The global R&D spend in 2015 was estimated at $141 billion,[2] and analyses have estimated that just over 50% of R&D spend can be allocated to clinical research costs.[3,4]

Pharmaceutical companies and contract research organizations (CROs) have access to a variety of data sources to support finding and evaluating clinical trial sites, but these data are often spread across multiple internal and external systems. Because the cost to acquire data as well as the time and complexity required to integrate across these data sources is significant, companies often make suboptimal decisions related to study planning, feasibility and site selection.

Rather than continuing to individually amass disparate, costly data sources, innovative companies are shifting their focus toward data integration and data sharing for the purpose of driving better decision-making, which, in turn, offers benefits to both researchers and investigators.

In a previous article,[5] the authors established a hypothesis regarding the potential benefits likely to accrue to organizations that choose to collaborate on investigator information and leverage technology to view this integrated information:

- More informed protocol planning and country selection
- Increased access to investigators for feasibility and site identification
- Elimination of the need for staff to integrate information across data sources
- Faster and more predictable recruitment through better matching of investigators to protocols
- Cross-sponsor access to good clinical practice (GCP) training dates (and decreased time/costs for companies that waive training based on mutual recognition)

In this study, we begin the process of quantifying the potential value of cross-company collaboration, with a focus of looking at the impact of data integration and data sharing on study planning, site selection, site start-up and internal master data management.

Methods

To quantify the value of cross-company collaboration on study planning and investigator selection, a return on investment (ROI) model was developed based on the experience of pharmaceutical companies using the DrugDev SiteCloud platform to integrate disparate sources of clinical trial information and share data. A description of the service evaluated in this article appears in Figure 1 on facing page.

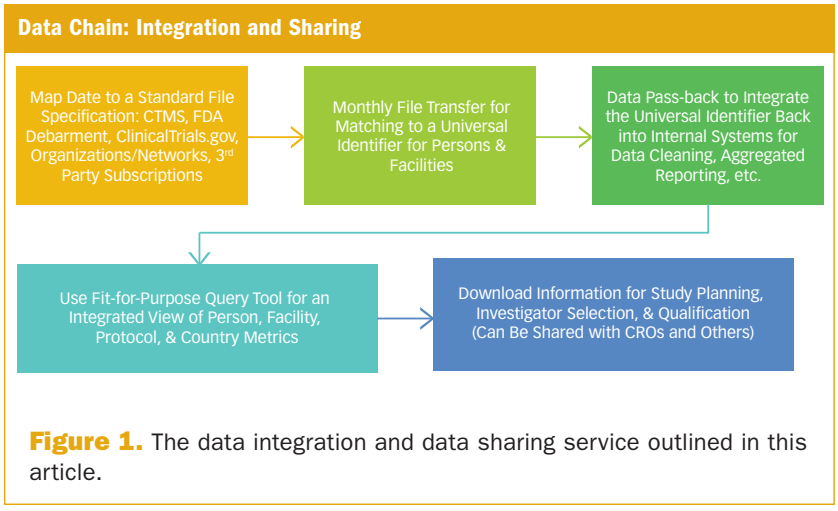


Figure 1. The data integration and data sharing service outlined in this article.

Data integration & data sharing service

An external consultancy, Hobson & Company, was engaged to facilitate the development of the ROI model using the following four step process:

1. **Internal interviews:** Five expert interviews were conducted with internal stakeholders representing multiple functional areas, including sales, marketing and subject matter experts. The objective of these interviews was to develop a hypothesized set of benefits that customers might expect to see from the data integration and data sharing solution described in Figure 1.

2. **Customer feedback:** In-depth interviews were conducted with 13 pharmaceutical company and CRO customers. The data provided by the customers was qualitative in nature and was collected during one-hour telephone interviews where customers were asked about the impact of data integration and data sharing on various areas of their business. The interviews sought to understand the key challenges experienced prior to data integration/sharing and the resulting sources of value and business improvement metrics post-implementation. The customers provided this information with the understanding that their responses would be shared but that their identity would remain confidential.

3. **Model development:** Based on the findings from the customer interviews, a final set of benefits was agreed, and a draft version of the ROI model was completed. Because the interviews revealed that the type and magnitude of benefits varied across customers, the model was constructed to capture a standard set of inputs and then allowed customers to tailor which benefits were included in the analysis and the magnitude of the value of each benefit. The draft ROI model was validated by one existing customer who provided perspective on the completeness, relevance and logic flow of the tool.

4. **Model implementation and refinement:** The ROI model has been implemented with several pharmaceutical company clients. During this implementation, the customer provided their actual information to input into the model including, but not limited to: number of studies per year, average duration of studies, average number of sites per study, time to do various activities, annual staff salary associated with activities, overhead rate and discount rate. A conference call was then scheduled to configure the benefits and outputs to reflect the value that each individual company could expect from data integration and sharing. Based on feedback received during actual implementation, small refinements have been made to the baseline value estimates included in the ROI model.

> **Innovative companies are shifting their focus toward data integration and data sharing for the purpose of driving better decision-making.**

Results

Benefits

Results from customer interviews suggest that data integration and sharing has the potential to increase operational efficiencies, decrease budget expenditures and enhance investigator engagement. Table 1 (see page 28) depicts the final list of benefits that emerged from the process.

In the actual use of the ROI model to date, four benefits from the list in Table 1 have been included across all customer implementations:

- Decrease the number of rescue sites potentially needed
- Decrease time spent by staff and clinical research associates (CRAs) on site start-up
- Decrease IT time/costs of facility and investigator data mastering
- Increase investigator engagement.

In contrast, two of the benefits in Table 1 were included by less than 30% of companies using the model:

- Reduce the number of protocol amendments
- Reduce over-recruitment of patients

Discussions with companies using the model suggest that these benefits were not included primarily because the company has already analyzed these processes and put in place process improvement measures to realize savings in these areas.

Value

For each benefit presented, Table 2 (see page 31) summarizes the value driver, median and range of metrics provided by customers using the model.

Advantages & Value Proposition	
BENEFIT	**VALUE**
1. Reduce time spent prioritizing/selecting investigators	Achieved through: 1) an integrated view across data sources, 2) more up-to-date contact information, and 3) more robust site-level data
2. Decrease the number of rescue sites potentially needed	By combining all data sources into one view and sharing data, researchers can conduct better study planning (country selection, timelines) and better matching of the right investigator to the right study
3. Decrease the cost and time associated with start-up of rescue sites	
4. Decrease time spent by staff and CRAs on site start-up	Collection, display, and sharing of start-up documents, including GCP training dates, GCP certificates, CVs, and site profile forms
5. Reduce the number of protocol amendments	Ability to create more realistic protocols through the upfront conduct of more robust study planning for country selection, and prediction of recruitment timelines based on internal and shared site-level performance data
6. Decrease IT time/costs of facility and investigator data cleansing/mastering	Decrease the need for investment in data cleaning and mastering by accessing the Golden Number for facilities and persons (unique identifier)
7. Reduce the number of non-performing sites	Better matching of the right site to the right protocol based on access to more data for known investigators as well as visibility into more investigators. In addition, data sharing allows CRAs/start-up staff to have insight into a site's broad study experience when making a selection decision/interacting with a site
8. Reduce over-recruitment of patients	Better matching of the right site to the right protocol based on access to more data for known investigators as well as visibility into more investigators. Through data integration and data sharing, researchers can also conduct better study planning (country selection, predicted recruitment timelines) and decrease the over-recruitment of patients at an individual site level, a common practice used today to compensate for non-enrolling sites
9. Increase investigator engagement	Approaching investigators with studies more suited to their interest/experience; reducing the administrative burden of site selection and start-up; implementing more realistic sponsor timelines; and engaging investigators earlier in the protocol development process will all contribute to increased investigator satisfaction, better engagement throughout the study, and decreased start-up times. Broadly, having a positive study experience will hopefully result in more investigators choosing to continue to participate in clinical research

Table 1. The benefits that result from a data integration and sharing approach.

Net present value of savings for a sample company

In this section, we estimate the net present value of the savings achievable over a five-year period by a sample organization that has an average of:

- 40 trials a year, 70 sites per trial, and 385 patients per trial
- 7.5 rescue sites per study with a start-up cost of $20,500 per site
- 18% of sites that don't enroll
- 10% cost of capital

Based on the medians above, we would expect a net present value for the sample company of $8.2 million over a five-year period.

Figure 2 (see page 30) presents a breakdown of this savings by benefit. As illustrated, for the sample organization, reducing the number of non-performing sites and increasing investigator engagement represent the majority of the value.

Limitations

The fact that the customer findings related to the benefits are anecdotal in nature, and are not necessarily based on actual documented savings is the greatest limitation of the model. That said, the sample organization inputs and outputs do reflect feedback from customers who are currently using and/or are very familiar with this system that provides data integration and cross-company data sharing. As such, we believe the results from the model do represent a good illustration of the actual savings companies would expect to see.

Generalizability is another limitation of this model. Every company that has used the model is different and this, along with a limited sample size of companies using the model, does mean it is difficult to generalize the findings. Customers have differing number of studies and designs (e.g., sites/patients) based on variation in therapy area. Differences in internal initiatives and SOPs also impact the benefits being selected or excluded as well as the value associated with each driver.

It is also important to note that while the model illustrates the total value created, some of the benefits documented may not translate into an actual reduction in annual expenditures (e.g., productivity gains do not always translate into

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Moderator:

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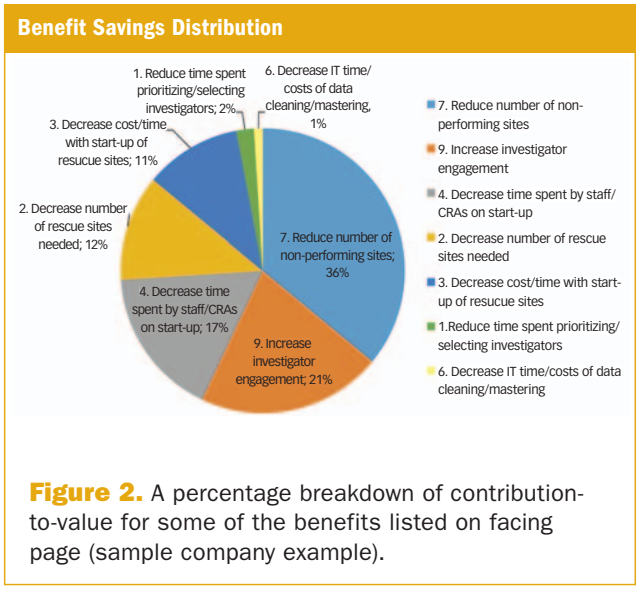

Figure 2. A percentage breakdown of contribution-to-value for some of the benefits listed on facing page (sample company example).

cash savings). Nevertheless, the dollar value assigned by the model can be thought of as an "operational capacity gain," where the time spent previously managing certain tasks can now be redeployed against other activities that may have otherwise required additional staffing.

Finally, we had great difficulty in quantifying one of the benefits: **Decrease IT time/costs of facility and investigator data mastering**. As discussed earlier, all customers using the ROI model found value associated with this benefit, but there was also agreement that the value resulting from the model is an under-estimate of what will likely be realized by most companies. This is primarily due to the fact that the value estimation is focused on a decrease in time spent on cleaning data, when the benefit to the organization extends well beyond study planning and site selection into other areas such as consolidated reporting for aggregate spend, master service agreement (MSA) negotiation, etc. (especially for companies who have grown through mergers and acquisitions and, as a result, have multiple clinical trial management systems).

Discussion

This paper describes an attempt to quantify the potential value of cross-company collaboration, with a focus of looking at the impact of data integration and data sharing on study planning, site selection, site start-up and internal master data management. While the value of data integration and sharing will vary depending on company characteristics, we estimate net present value over a five-year period to be approximately $8 million. Nearly 75% of this value to an average company is driven by three benefits: reducing the number of non-performing sites, increasing investigator engagement, and decreasing time spent by staff and CRAs on site start-up.

The concept of cross-company data sharing to support trial planning and site selection applies to many solutions across different areas of industry. Examples of such initiatives include networks of research sites (e.g., ACRES[6] and the Global Health Network[7]), genomic data-sharing initiatives (e.g., NIH Genomic Data Sharing[8] and the UK's Genomics England[9]), and industry collaborative projects (e.g., Investigator Databank,[10] TransCelerate's Placebo and Standard of Care Data Sharing Initiative,[11] Investigator Registry[12] and Shared Investigator Platform[13] and the European Innovative Medicines Initiative[14]).

> **While difficult to quantify, the hope is that cross-company collaboration could ultimately affect the high turnover of clinical trial investigators.**

The intent to look for efficiency gains from data integration and interoperability in various cross-company collaborations is also reflected at the company clinical trial management system (CTMS) level. Customers are demanding a greater degree of interoperability from their CTMS providers, and, thus, today's CTMS solutions are increasingly offering integration with multiple clinical systems (e.g,. electronic data capture, randomization and trial supply management, interactive voice-response systems and financial information).[15]

Over and above the five-year savings documented in the model, all customers believe strongly that data integration and data sharing can have a very large impact on investigator satisfaction. While difficult to quantify, the hope is that cross-company collaboration could ultimately affect the high turnover of clinical trial investigators. Working with unrealistic sponsor expectations can have a significant impact on investigator satisfaction, leading to turnover. Approaching investigators with studies that are better suited to their interest/experience, engaging investigators earlier in protocol development, and reducing the administrative burden of site start-up will contribute to better engagement not only in the start-up period documented in the model, but also throughout the entire study. Ultimately, having a positive study experience will hopefully result in more investigators choosing to continue to participate in clinical research.

Conclusion

This study has shown that companies looking for ways to reduce non-performing sites should consider investing in technology that enables integration of multiple sources of investigator, experience and trial recruitment data. Integrating a view across these sources is likely to result in more rapid recruitment as well as fewer zero-enrolling sites. For those organizations willing and able to share site study history and

Impact Measures

BENEFIT	VALUE DRIVER	MEDIAN	RANGE
1. Reduce time spent prioritizing/selecting investigators	% reduction in time spent selecting sites	10%	0% – 25%
2. Decrease the number of rescue sites potentially needed	% reduction in the number of rescue sites needed	5%	3% – 10%
3. Decrease the cost and time associated with start-up of rescue sites	# of days decrease in timeline and associated costs	1	0 – 5
4. Decrease time spent by staff and CRAs on site start-up	% reduction in time spent on training & document collection	10%	3% – 50%
5. Reduce the number of protocol amendments	# of protocol amendments avoided	NA*	0 – 0.25
6. Decrease IT time/costs of facility and investigator data cleaning/mastering	% reduction in time spent on data cleaning/mastering	20%	5% – 50%
7. Reduce the number of non-performing sites	Decrease in number of non-enrolling sites	1	0 – 2
8. Reduce over-recruitment of patients	% reduction in patient over-recruitment	NA*	0 – 5%
9. Increase investigator engagement	# of days reduction in start-up time	2	1 – 5

**Less than 50% of customers assigned value to Benefits 5 and 8.*

Table 2. The estimated value associated with each solution benefit.

metrics, access to more robust site-level performance will generate even more efficiencies than data integration alone. And, the more organizations that agree to share data and collaborate on investigator-facing activities, the simpler clinical trial operations will be for investigators, which, in turn, has the potential to address another critical issue faced by the industry today: investigator turnover.

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Africa a Ripe Proving Ground for Digital Health

David Blackman

A proposed operational framework to support digital- and mHealth-based clinical trials in Africa.

Knowledge transfer in clinical drug development has followed a well-worn path from the mature research environments of North America and Europe to the developing regions of Eastern Europe, Asia and Latin America. Digital research technologies could well turn the tables, giving emerging nations an advantage in pioneering digital-based, operational models for 21st century clinical trials.

Digital research platforms—including the current integration of wearable mobile health (mHealth) devices with smartphones to facilitate data collection—promise improvements in both data quality and cost efficiency. Their adoption has been slowed by the need to integrate these fast-evolving technologies within existing research infrastructure and practice. Environments free of legacy systems have the advantage of building comprehensive, "right-by-design" digital and mHealth models spanning all trial operations. Such approaches will be best able to optimize the benefits of digital platforms to improve data accuracy and reduce reliance on costly clinic-based operations. At the same time, digital platforms will facilitate clinical trials in underserved populations where lack of infrastructure has made traditional research models unfeasible.

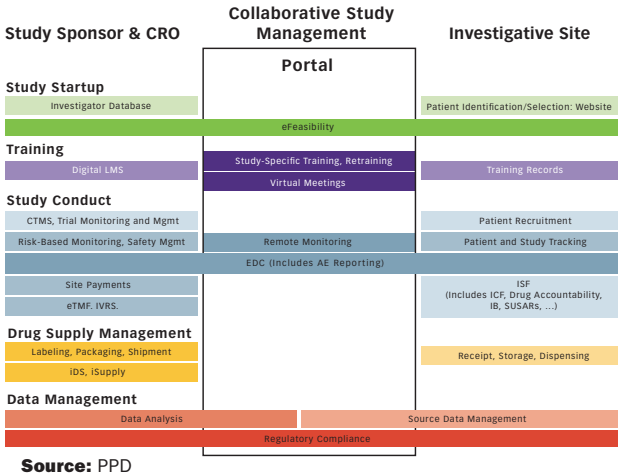
Africa's blank slate

While there are wide variations in maturity of industry, infrastructure and clinical capabilities, many believe the cumulative "blank-slate" opportunity is greatest in Africa, which accounts for about 15% of the world's population but hosts only an estimated 0.9% of global clinical trials.[1] Inadequate medical and research infrastructure has made clinical trials cost-prohibitive. Africa's research landscape is maturing, however, due to economic growth and the rise of non-communicable diseases more characteristic of developed regions.

Africa's population is expected to reach 2.4 billion by 2050.[2] By 2020, non-communicable diseases, including cancer, diabetes, hypertension and cardiovascular disease will account for 65% of mortality.[3] As demand for therapies to treat these conditions grows, Africa's economies are growing as well. GDP is projected to rise to $3.3 trillion in 2020. And, according to a 2015 McKinsey report, Africa's $20.8 billion pharmaceutical market could reach $60 billion by 2020.[4]

Africa's research capabilities are now primed to enable digital trials designed for this special environment. An increasing number of major clinical trials are being supported by collaborations like The World Health Organization's Special Programme for Research and Training in Tropical Diseases (TDR) and the European and Developing Countries Clinical Trials Partnership (EDCTP) are setting the stage. A 2007 EDCTP report identified qualified Phase II/III clinical sites in 19 sub-Saharan countries with capability to conduct trials in tuberculosis (TB), malaria and HIV.[5] Infrastructure now can sustain studies like Wyeth's 2009 river blindness trial in Ghana, Liberia and Democratic Republic of Congo,[6] and the TDR cosponsored TB trial involving 1,800 patients across five countries, published in 2014.[7]

Digital Capabilities Framework



Source: PPD

Figure 1. A framework of digital capabilities for clinical studies across three operational spheres.

Infrastructure Needs

Location	Electricity	Network Connectivity	Security
Central study office	Need continuous power ensured by backup power supply to avoid loss of critical documents or data due to power loss.	Need continuous, reliable Internet access to support transmission of a significant volume of data and documents between central study office and sponsor.	Need physical security (locked office, locked cabinet, access management) to prevent loss or theft of digital equipment containing essential study data.
Study field offices	Need regular power; intermittent power access may be acceptable. Study equipment used at this location (imaging, lab) may require power backup.	Need access to regular but not necessarily continuous power. Intermittent power may be acceptable for regular transfer of primary study data.	Need physical security (locked office, locked cabinet, access management) to prevent loss or theft of digital equipment that may contain essential study data.
Field operations	Need at least daily access to electricity for charging mobile devices.	Need at least daily access to mobile network for transfer of study data.	Implement access management to control access-essential study data.

Source: PPD

Figure 2. Electricity and Internet requirements by sites of study operation.

Digital research platforms have the potential to create a fully capable digital environment in Africa, especially when they incorporate wearable devices and telemedicine approaches that are designed to simplify the participation in a trial for patients and connect them to the best global scientific research regardless of their location. For instance, medical grade wearable sensors integrated with smartphones now enable accurate, continuous real-world data collection, independent of sparsely located clinical sites. Smartphones are widely used in African healthcare settings. Some 21 million new mobile subscribers were tallied in the first quarter of 2015 alone.[8]

Using today's available technologies, the following discussion proposes an operational framework to support African-based digital studies across trial operations—from site initiation and patient enrollment through study conduct, data collection and site closeout.

A digital framework for Africa

In Africa, digital research platforms will have three fundamental requirements: cost-effective digital technologies to support operations across clients, service providers and investigative sites; reliable electrical power and Internet connectivity; and regulatory acceptance of and study compliance with digital technologies and approaches.

Figure 1 outlines a framework of digital capabilities currently used to conduct studies across three operational spheres: activities conducted by the client; activities conducted in collaboration with technology and service providers, primarily contract research organizations (CRO); and activities conducted by investigative sites. These technologies enable pre-trial intelligence (study feasibility and identification/recruitment of investigator sites); training for site personnel; study management; document management; drug supply management; and data management.

Using these digital technologies, three operations centers would be sufficient to conduct all trial activities:

- A central study office—such as a project office at a university teaching hospital—would be responsible for study coordination.
- Study field offices—either central or remotely located—would conduct subsets of activities for multiple patients. These include central laboratories, imaging facilities and primary health clinics supporting treatment and follow-up.
- Field operations would conduct small subsets of tasks for a small set of patients. For example, community health workers administering surveys or collecting data during visits to patients' homes.

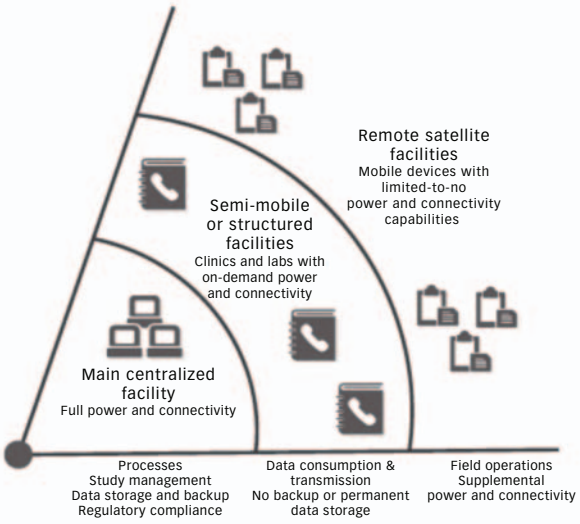
Figure 2 details the necessary infrastructure requirements for participating study centers, which includes access to electrical power, network Internet connectivity, physical security to protect study materials and data, and the ability to control access to essential data.

Access to power and Internet communications typically are barriers to conducting trials in Africa. The digital platform suggested here would increase the feasibility of African-based trials since lower levels of access are sufficient for different operational centers. Only the central study office would require continuous power and connectivity. Field offices and operations would need daily access but could fully meet study responsibilities with intermittent power and Internet access, as illustrated in Figure 3 (see page 34).

Evolving regulation

While not losing sight of the challenges that still need to be overcome to address political instability, corruption and the absence of reliable shipping and storage facilities for clinical trial supplies in some regions, Africa is evolving. The regulatory environment is maturing through standards and practices specifically pertaining to Africa with, for example, ethical guidelines developed by the Swiss Tropical and Public Health

Relative Infrastructure Requirements



Source: PPD

Figure 3. The requirements across three facility types.

Institute (Swiss TPH)[9] and a regional trial registry created by the Pan African Clinical Trials Registry (PACTR).[10]

Historically, sponsors have conducted African trials in compliance with the FDA, European Medicines Agency (EMA) and other global standards. Regulations are emerging to guide the implementation of digital approaches, but regulators are hard-pressed to stay current with fast-moving digital and mHealth technologies. FDA issued guidances in 2014 and 2015 presenting regulatory views on the use of mHealth devices in clinical trials.[11,12] Other pertinent guidelines include: FDA guidance on use of electronic source (eSource) data (2013)[13]; standards for eSource data standards of the Clinical Data Interchange Standards Consortium (CDISC)[14]; and EMA's reflection paper on eSource data and EDC tools (2010).[15]

Conclusion

This proposed operational framework for digital-based clinical trials in Africa is intended as a starting point toward three important goals: expanding drug development research in underserved African populations; laying the technology groundwork for developing and building scientific expertise; and piloting "right-by-design" digital research approaches in a blank-slate environment free of legacy infrastructures that slow adoption of disruptive methodologies. The technologies described in this article are available now. Their utility and benefits have been demonstrated, and they currently are used in clinical trials to improve data collection, data management, safety monitoring and informed consent. Africa offers a compelling opportunity to pilot digital and mHealth research platforms to revolutionize clinical trial operations worldwide.

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Phase III Trial Failures: Costly, But Preventable

Alberto Grignolo, PhD, Sy Pretorius, MD

An examination of recent failures in Phase III studies and innovative approaches to reduce risk.

Thomas Henry Huxley (1825-1895) once stated, "The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact." Indeed, in drug development not all ground-breaking scientific ideas translate into miracle cures. Biopharmaceutical companies around the globe strive to develop novel therapies to fulfill unmet medical needs, yet these efforts all too often die in development. Despite the numerous scientific, technological, and operational advances in R&D that would be expected to increase the efficiency and success of drug development, a significant number of clinical trials still fail to produce new, effective, and safe medicines.

Approximately 70% of Phase II trials are unsuccessful.[1,2] Although this percentage might seem high, failure of early-phase trials is expected to some extent, as these trials are "exploratory," "proof of mechanism," and "proof of concept" trials in patients.[3] What is unexpected, however, is the percentage of "confirmatory" Phase III trials that fail—about 50%.[1,2] Theoretically, if early-phase trials provide the necessary criteria for moving a drug program to Phase III testing, relatively few Phase III trials should fail; but that is not the case.

In a recent PAREXEL analysis,[4] we collected and evaluated data on 38 Phase III failures from mid-2012 through 2015 from a variety of publicly available sources (It is important to note that this list may not be exhaustive and may not include all of the Phase III trials that failed in this time period). As indicated in Table 1 (see facing page), these trials failed to meet primary or secondary efficacy endpoints; Phase III trials that failed due solely to safety issues are not included. These 38 failed trials collectively enrolled nearly 150,000 patients.

Peeling the onion: What are the drivers behind these Phase III failures?

Several groups have sought to analyze data from failed clinical trials to uncover the underlying trends and potential drivers of Phase III failures. Selected trends are discussed below.

1. A study by the Tufts Center for the Study of Drug Development (CSDD)[5] evaluating clinical trials from 2000 to 2009 found that the three most common reasons that drugs or trials fail in Phase III of development are (see Figure 1 on facing page):

- Efficacy (or rather lack thereof) — i.e., failure to meet the primary efficacy endpoint
- Safety (or lack thereof) — i.e., unexpected adverse or serious adverse events
- Commercial / financial — i.e., failure to demonstrate value compared to existing therapy

2. New molecular entities (NME) versus all drugs. A study by BioMedTracker (BMT) and the Biotechnology Industry Organization (BIO) evaluated R&D projects involving more than 9,500 different drug and biological products from 2004 to 2014.[1] In each phase analyzed, the failure rates of trials involving NMEs were higher than trials involving all drugs, and the difference was greatest between Phase III development and submission of regulatory applications (See Figure 2 on page 38). Among the Phase III trials analyzed, only 61% of NME trials succeeded in moving to the application phase

Phase III Failures: Lack of Efficacy

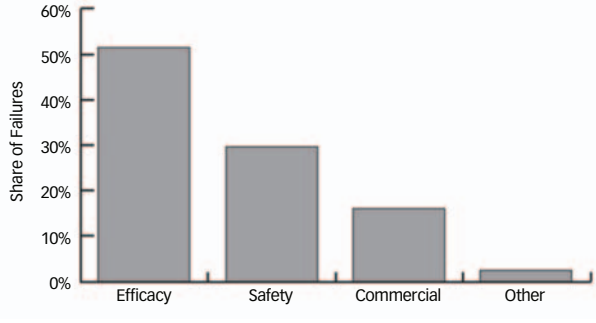
THERAPEUTIC AREA	NUMBER OF TRIALS	PATIENTS ENROLLED	AGENTS/COMBINATIONS TESTED
CARDIOVASCULAR *Indications studied: acute coronary syndrome, acute heart failure, atherosclerotic disease, cardiovascular cell damage*	6	**58,759**	darapladib, evacetrapib, losmapimod, otamixaban, serelaxin
ENDOCRINE/METABOLIC *Indication studied: diabetes*	4	**38,066**	aclerastide, aleglitazar, basal insulin peglispro[a], saxagliptin
ONCOLOGY *Indications studied: breast cancer, castrate-resistant prostate cancer, colorectal cancer, leukemia, non-small cell lung cancer, lymphoma, ovarian cancer, uveal melanoma*	18	**19,856**	alisertib, cabozantinib, dacomitinib, enzastaurin, etirinotecan pegol, ganetespib + docetaxel, iniparib, lapatinib + trastuzumab, MAGE-A3, motesanib, onartuzumab, ramucirumab, selumetinib + dacarbazine, trebananib + paclitaxel, True Human™ antibodies[b], vintafolide, vosaroxin + cytarabine
PULMONARY *Indication studied: chronic obstructive pulmonary disease*	1	**16,485**	fluticasone furoate + vilanterol
CENTRAL NERVOUS SYSTEM *Indications studied: Alzheimer's disease, depression, schizophrenia*	5	**9,140**	bitopertin, edivoxetine, pomaglumetad methionil, solaneumab
AUTOIMMUNE *Indications studied: ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus*	4	**3,378**	apremilast, tabalumab, vercirnon
TOTALS	**38**	**145,684**	**34 AGENTS/COMBINATIONS**

[a]*Program terminated due to focus on other drugs in portfolio and to assess effects on liver fat.*
[b]*Phase III trial terminated due to insufficient number of per-protocol patients available for primary endpoint analysis and protocol violations*

Source: PAREXEL Analysis

Table 1. Phase III trials during 2012-2015 that failed to meet primary or secondary efficacy endpoints.

Reasons for Failures



Source: Tufts Center for the Study of Drug Development (CSDD)

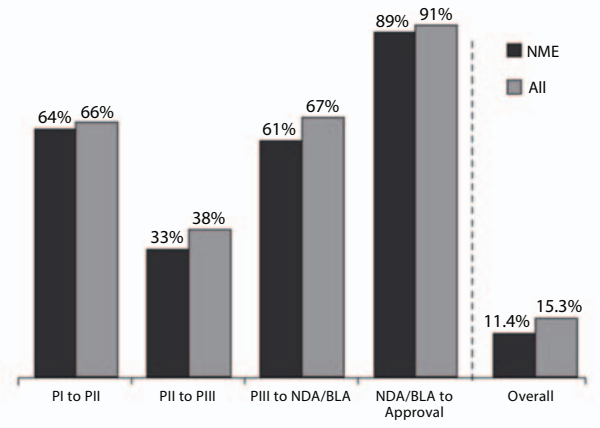
Figure 1. The reasons attributed to Phase III clinical trial failures by percentage.

(39% failure rate), whereas 67% of all drug trials moved to the application phase (33% failure rate). The high failure rate of Phase II trials reported in that analysis (62% and 67%, respectively) is not unexpected for exploratory trials.

3. Failure rates differ by therapeutic area. The BMT/BIO study also found that clinical trial failure rates differ by therapeutic indication.[1] Among the Phase III trials evaluated, oncology and cardiovascular trials had the highest failure rates (data not shown). Comparing failures for oncology and non-oncology trials specifically, failure rates for these indications differed more significantly at later stages of development (See Figure 3 on page 38). The oncology trials failed more often than non-oncology trials during the Phase II-to-Phase III transition and, in particular, from Phase III testing to regulatory submission (48% failure rate for oncology trials vs. 29% for non-oncology trials). The higher failure rate for oncology trials might be due to the inclusion of survival endpoints and the need to show efficacy by an improvement in overall survival.[6]

4. Failure rates differ by type of molecule. A study by the Tufts CSDD found that the probability of success for clinical trials of small molecules is lower than for trials of large molecules (see Figure 4 on page 39).[7] Among the Phase III trials analyzed, only 61% of studies involving small molecules progressed from Phase III testing to the regulatory application phase (39% failure rate). Trials of large molecules, however, were more successful in moving to the application phase, with a success rate of 74% (26% failure rate). The study also found that within the large-molecule subtypes, failure rates for recombinant proteins and monoclonal antibodies were similar overall, but recombinant proteins failed more often than monoclonal antibodies in the transition from Phase III testing

Success Rates by Phase

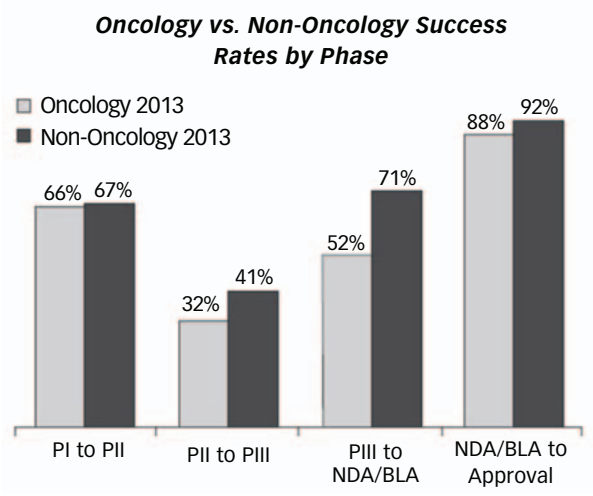


Note: Each phase success rate represents the rate at which products successfully completed that phase and moved to the next phase.

Source: BMT/BIO

Figure 2. The difference in rate success of trials involving NMEs was greatest between Phase III development and submission of regulatory applications.

Success Rates by Therapeutic Indications



Source: BMT/BIO

Figure 3. Failure rates for oncology and non-oncology trials differed more significantly at later stages of development.

to regulatory review (34% failure rate for recombinant proteins vs. 13% for monoclonal antibodies; data not shown).

The European Center for Pharmaceutical Medicine (ECPM) organized a seminar in September 2014 titled "Why Clinical Trials Fail?" Based on presentations delivered by various experts at the seminar, we have grouped the drivers behind Phase III failures identified by these experts into six categories: basic science, clinical study design, dose selection, data collection and analysis, operational execution, and other. Table 2 (see facing page) provides examples of specific events in each category that could lead to Phase III failure.

Impact of Phase III failures: Human and financial

The effects of Phase III failures are significant, with the most poignant being the impact on human lives and financial cost. First and foremost is the negative impact on the thousands of patients who enroll in clinical studies hoping to find a viable treatment option. As mentioned previously, PAREXEL's analysis revealed that in a relatively narrow time frame (2012-2015), nearly 150,000 patients had enrolled in Phase III trials that eventually failed. Most of these patients had cardiopulmonary diseases, diabetes mellitus, or cancer.[4] Patients who participate in clinical trials often have difficult-to-treat or later-stage diseases with few, if any, standard treatment options. For many of these patients, time may be running out, and a clinical trial is the last option for a potential cure or prolongation of life. Thus, the impact of failed drug trials can be widespread and may worsen patient prognosis, quality of life, and emotional well-being.

Not surprisingly, failures of large Phase III trials also result in a material financial burden to biopharmaceutical companies and are a contributor to poor capital productivity. Considering the substantial financial investment in R&D, few new drugs are being approved by regulators. One study found that for every billion U.S. dollars spent on R&D, the number of new drugs approved has decreased by approximately 50% every nine years since 1950 (inflation-adjusted).[8] And, the financial consequences of failed drug development often go beyond R&D. An examination of the most impactful Phase III failures of 2014 found that these failures resulted in the termination of drug programs and employees as well as financial losses for investors, as shown in Table 3 (see page 40; note that only some of these failures are also listed in Table 1). With slower growth in R&D spending,[9] it is important that biopharmaceutical companies use the limited funds and resources efficiently and effectively to get drugs to market and provide new medicines that meet unmet medical needs.

Selected strategies to reduce the risk of late-stage failure

Although no simple solution exists yet for preventing Phase III failures to confirm the efficacy of a new drug or biologic, several approaches have been and are currently being developed to reduce the risk of such failure. Given our unique perspective in working with hundreds of companies across thousands of clinical trials and compounds, we and numerous colleagues at PAREXEL are exposed to these approaches on a daily basis and briefly highlight some of these in the next sec-

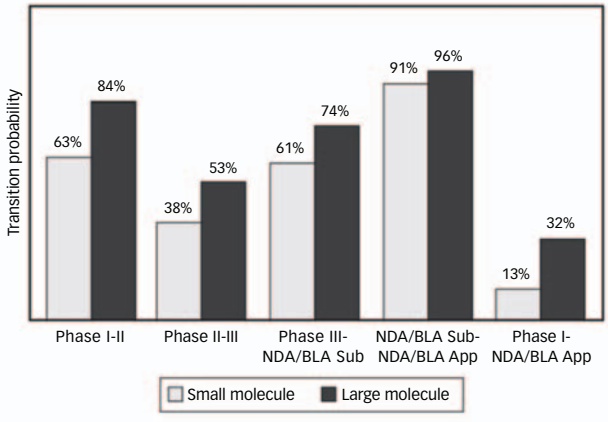
Failure Triggers

DRIVERS OF FAILURE	EXAMPLES
Inadequate basic science	• Beneficial effects in animal models not reproduced in humans • Poor understanding of target disease biology
Flawed study design	• Patient population definition changed from Phase II to Phase III • Phase II surrogate endpoint not confirmed by Phase III clinical outcomes • Insufficient sample size
Suboptimal dose selection	• Inadequate dose finding in Phase II • Poor therapeutic indices
Flawed data collection and analysis	• Phase II "false positive" effects were not replicated in Phase III • Overoptimistic assumptions on variability and treatment difference • Missing data; attrition bias; rater bias • Wrong statistical tests; other statistical issues
Problems with study operations	• Data integrity issues; GCP violations • Recruitment, dropouts, noncompliance with protocol • Missing data; unintentional unblinding
Other	• Insufficient landscape assessment of current standard of care and precedents

Source: European Center for Pharmaceutical Medicine; PAREXEL Analysis

Table 2. Specific events in key areas of clinical trial conduct that can result in Phase III failure.

Success Rates by Molecule Type



Source: Tufts Center for the Study of Drug Development (CSDD)

Figure 4. According to a study, the probability of success for clinical trials of small molecules is lower than for trials of large molecules.

tion. These strategies can be implemented during the entire development process, in specific phases of development, and/or during clinical trial design.

Applying more rigor to the overall development process

Over the past few years, most drug development companies have established and adopted more disciplined protocol, progress and portfolio review frameworks. In 2011, AstraZeneca aimed to overhaul its R&D process to improve the health of the organization and increase the chance of success of its Phase III trials. By evaluating its small-molecule drug projects over a five-year period (2005–2010), AstraZeneca identified the factors associated with project success and developed a framework that now drives its development process. The 5R framework guides R&D teams in identifying the right target, the right tissue, the right safety, the right patients, and the right commercial potential (See Figure 5 on page 41).Having the right culture—i.e., a culture where the facts and data are confronted with brutal honesty, and courageous kill-early decisions are encouraged where appropriate—is an important, additional dimension to this framework.[10] Applying more rigor and discipline to the development process holds potential for weeding out likely failures earlier in the process, thereby reducing Phase III failure rates.

Adequate Phase II testing

Many Phase III trials fail because of a fundamental lack of understanding of the mechanisms of action of NMEs. To address this issue and improve the chance of NMEs being successful during Phase II testing, Pfizer performed an analysis of 44 Phase II programs during a four-year period (2005-2009) to identify factors associated with success.[11] The result of that analysis led to the "Three Pillars of Survival" framework that helps the R&D teams determine three key elements that increase the likelihood of an NME surviving Phase II testing and moving on to Phase III testing: Pillar 1 involves exposure of the drug to the target site of action; Pillar 2 involves binding of the drug to the target; and Pillar 3 involves expression of pharmacology (see Figure 6 on page 42). Rushing to get to Phase III without adequate understanding of these three criti-

cal components is risky and more often leads to unpleasant surprises in Phase III. Not only does this proposed approach in Phase II make intuitive sense, but we also believe that it holds potential for reducing late stage failures.

Optimized Phase III Clinical Trial Design

Flaws in clinical trial design are a major driver of Phase III failures. Several strategies have been developed for optimizing trial design. The next section aims to highlight a few of them:

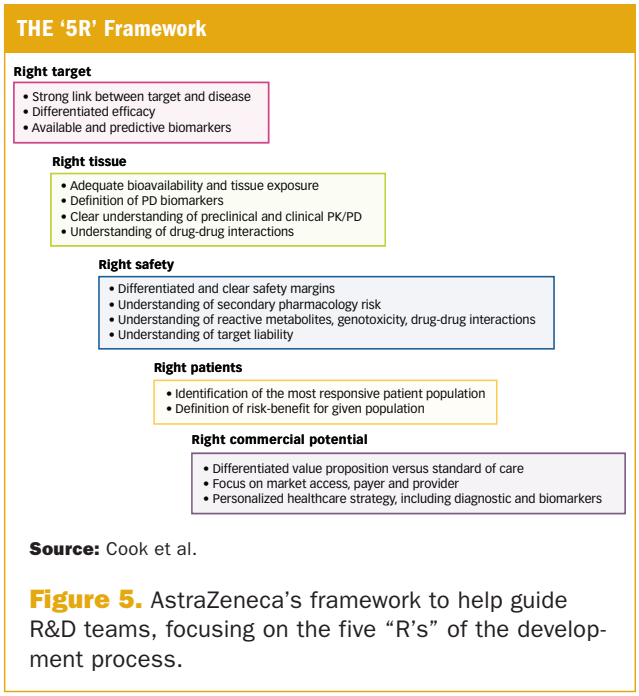
- More rigorous **protocol review and optimization** is an approach that many companies are employing in varied degrees ranging from stage gate reviews and sign-offs by various internal committees to live, in-practice simulations of protocols to identify and resolve potential glitches proactively. Typically, a number of trade-off decisions need to be made in the compilation of most Phase III protocols—e.g., will the protocol include a specific secondary objective that has commercial value but potentially prolongs the duration of the study? Identifying and quantifying the impact of these trade-offs is helpful in designing better protocols. Likewise, in the right capable hands, the vast amount of data available in public sources (e.g., Clinicaltrials.gov) can often be harnessed to determine what worked well and what did not.
- **Modeling and simulation** have contributed to regulatory approval and labeling decisions in recent years and are currently being employed as a potential solution for mitigating late-stage failure risk.[12] In a review of 198 applications submitted to the FDA between 2000 and 2008, modeling and simulation was found to provide pivotal or supportive insights into effectiveness and safety that contributed to the approval of 126 applications.[13] Additionally, it provided information on dosage, administration, and safety that supported 133 labeling decisions. The FDA encourages sponsors to incorporate quantitative modeling and trial simulation in the drug development plan and to seek regulatory guidance on these strategies through participation in an end-of-phase 2A (EOP2A) meeting.[14] The EOP2A meeting provides the sponsor with an opportunity to discuss modeling and simulation plans and receive feedback from the FDA on how to optimally implement these strategies to quantify the exposure-response relationships and select appropriate doses for Phase III trials. Modelling and simulation is currently being used more broadly than just for the selection of an optimal dose. Modeling and simulation of various clinical trial designs is one such example that is being used in an effort to design optimal Phase III studies.

Financial Consequences of Phase III Failures

SPONSOR	DRUG	INDICATION	CONSEQUENCES OF FAILURE
Exelixis	**cabozantinib**	metastatic castration-resistant prostate cancer	• 150 jobs (65% of workforce) terminated • $6-$7M in termination costs (95% charged in 3Q 2014; 5% in 1Q 2015) • Reversed $2.1M of previously recorded stock-based compensation expenses • Cancelled 692,896 stock options due to unrealizable performance objectives
OncoGenex Pharmaceuticals/ Teva Pharmaceutical Industries	**custirsen**	metastatic castration-resistant prostate cancer	• Share price fell 60% • Collaboration with Teva terminated
GlaxoSmithKline	**MAGE-A3**	Non-small cell lung cancer	• Share price fell almost 2% • Development halted
Nymox Pharmaceutical	**NX-1207**	benign prostatic hyperplasia	• Share price fell nearly 82% • Development halted
Regado Biosciences	**pegnivacogin + anivamersen**	coronary artery disease undergoing percutaneous coronary intervention	• Share price fell 60% • 20 jobs (60% of workforce) terminated • $2M in termination costs charged in 4Q 2014
Eli Lilly	**tabalumab**	systemic lupus erythematosus	• Development halted • $63M in termination costs charged in 3Q 2014
Merck & Co./ Endocyte	**vintafolide**	platinum-resistant ovarian cancer	• Share price fell 62% • Withdrawal of marketing applications for vintafolide & companion imaging products

Source: Modified and reprinted with permission from GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, February 2015, published by GEN Publishing, Inc., New Rochelle, NY.

Table 3. The financial and other company-related losses resulting from a selection of Phase III trial failures in 2014.



Source: Cook et al.

Figure 5. AstraZeneca's framework to help guide R&D teams, focusing on the five "R's" of the development process.

- **Adaptive designs** are gaining momentum as a way to reduce failure risk. This is, in large part, due to the fact that these adaptive designs provide an opportunity to assess interim data and to sense-check some of the initial uncertainties or assumptions that were made at the outset of the trial.[15,16] More importantly, these provide an opportunity to change course during a trial and to correct these incorrect assumptions in a prospectively planned manner that does not jeopardize statistical validity and the operational integrity of the trial.[17]
- **Biomarkers** are being used increasingly to assess efficacy in a rapid and more objective manner.[18] A particular challenge associated with the use of biomarkers in clinical trials is the requirement to validate these biomarkers as relevant disease-modifying endpoints and correlate changes in these endpoints to clinically significant changes in disease progression.[19] Likewise, **enrichment strategies** often involving genotyping are being used increasingly to optimize the proposed study population to those individuals most likely to respond to the treatment under investigation.[20]

De-risking study execution

A number of approaches are currently being used to mitigate study execution risks. These include:

- Leveraging data from a variety of sources (e.g., electronic health records [EHR], prior site performance, central labs, etc.) to ensure that the selection of patients, sites, and countries are optimal. The impact of EHRs on clinical trials is carefully tracked by numerous interested parties, and it is not difficult to imagine the potentially transformative impact that these might have on clinical trials. At the same time, many industry insiders hold a somewhat skeptical view—especially about the accuracy of data in these systems.
- Ongoing surveillance of the quality of data being collected during a Phase III trial and tying this to a properly planned risk-based monitoring protocol allows companies to set certain quality triggers that would result in increased monitoring when and where needed. This is helpful in reducing execution risk, as errors at the site level are often discovered too late in the process—i.e., once the study is clinically completed and the database is locked. Often, at this time, very little can be done to salvage the situation and improve the quality and potential for success in the trial.

Completeness and clarity of submissions and interaction with regulatory agencies

Many drugs fail to get approved because the information submitted to the regulatory agency is insufficient to allow for a determination on safety and efficacy, not because the drug is actually unsafe or ineffective. A review of marketing applications for NMEs submitted to FDA from 2000 to 2012 revealed that about 50% of those reviewed failed to obtain approval during the first-cycle.[2] However, nearly 50% of these failed applications were eventually approved on resubmission after applicants addressed the FDA's concerns related to safety, manufacturing, and labeling. Delayed approvals and non-approvals may be reduced or prevented by seeking advice from regulators during the drug development process. The FDA offers sponsors and applicants the opportunity to schedule formal meetings at critical points in the development and regulatory process to discuss the plan and identify areas of concern that may need adjustment.[21]

Other bold/promising/theoretical/philosophical strategies that could reduce Phase III failures

Other areas that are currently being explored and could hold potential in reducing Phase III failure risk include:

- Replacement of the current gold standard, the randomized controlled trial, with real-world evidence
- Wearable devices that collect real-time data[22]
- Adaptive licensing
- Next-generation sequencing and improved understanding of the genetic basis of disease
- Basket/master protocols

Although Phase III failures cannot be eliminated, the risk of these failures can be reduced. The strategies discussed in this article may provide sponsors with some of the tools aimed at minimizing the risk of failure in their drug development plans.

Conclusion

We believe that the current failure rate in Phase III studies is unacceptably high, and that industry is keen on reducing this failure risk, although some in industry may believe that fail-

The 'Three Pillars of Survival'

- **Pillar 1:** Drug exposure at the target site of action is necessary to elicit a pharmacological effect over a desired time period.
- **Pillar 2:** Target occupancy is a prerequisite for expression of pharmacology and target modulation.
- **Pillar 3:** Functional modulation of the target is a prerequisite for expression of pharmacological activity to test the mechanism.

Source: Morgan et al.

Figure 6. Pfizer's framework to help determine three key elements that raise the likelihood of an NME surviving Phase II testing and moving on to Phase III.

ure is the price to be paid for innovation. As a first step, it is important to understand the reasons and root causes driving these failures. Our research identified recently failed Phase III studies that have enrolled nearly 150,000 patients. Based on data from our analysis and others, we have listed the main reasons why Phase III trials fail. In addition, and given our unique perspective in working with hundreds of sponsors across thousands of trials, we have highlighted some of the approaches that pharmaceutical companies are implementing in an effort to reduce these costly late-stage failures. Along with our colleagues in the pharmaceutical industry, we are optimistic about the potential of some or all of these approaches to improve the Phase III success rate.

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Interexpert Agreement on Adverse Events' Evaluation

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Study measures the differing judgments between clinical investigators and drug safety experts.

Safety surveillance is one of the core objectives of every clinical trial. It is based on registration and assessment of adverse drug reactions (ADRs), defined as noxious and unintended responses to a medicinal product related to any dose.[1] Not all ADRs are attributed to the study drug and one of the key characteristics of every ADR is causal relationship, or causality—whether the event under question is obviously related to the study drug, or at least such relationship cannot be ruled out. All available information about ADRs observed with the drug is captured in the Investigator's Brochure, and once the drug is approved for use—in the package insert. This makes assessment of causal relationship a key factor, as underestimation may subject potential patients to an unexpected and unnecessary risk, while overestimation might narrow indications and therapeutic use, or lead to dose modification (e.g., decreased dosage), which may lead to decreased efficacy.

The WHO-UMC assessment scale is meant as a practical tool for the assessment of case reports. It is a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.[2] Other algorithms are more complicated. Such scales have proved their validity, but have a general disadvantage—they are based on individuals' medical judgment and thus subjective. Experts may evaluate similar ADRs differently. Such disagreements have been reported previously and ranged from 51% to 95%.[3,4,5] These reports mainly compared judgments made by physicians or experts without analysis of possible reasons for disagreements. Herein, we compared the assessments of 50 ADRs made by four experts from a contract research organization (CRO medical monitors) and clinical trial investigators, analyzing the reasons for different evaluations.

Methods

Four drug safety experts, who were not medical oncologists, but had experience monitoring oncology trials independently, analyzed 50 consecutive (in terms of time of registration) blinded serious adverse events (SAE) from three Phase II-III clinical trials conducted in 2014-2015. The studies involved in patients with locally-advanced (inoperable) or metastatic non-small cell lung cancer (NSCLC). One of three trials was a placebo-controlled one and two studies were open-label. All patients, including those from the placebo arm, received one or two chemotherapeutic agents. All patients from the open-label studies received an investigational drug as a part of their chemotherapeutic regimen. Among the 37 cases from the placebo-controlled trial, 17 of the patients (46%) received the study drug and chemotherapeutic agent and 20 (54%) were administered the placebo and chemotherapeutic agent. The information for the SAEs was summarized in narratives, which included demography data, medical history, concomitant medications, study treatment with dates, the course of the AE, and the list of expected AEs for the particular study drug. The

investigator's assessment was deleted from the narrative, so the experts were unaware whether or not the AE was assessed by the investigator as an ADR.

For each drug-event pair, the questionnaire asked the experts to assess causal relationship based on the following criteria:

- Time to onset: incompatible/compatible/highly suggestive
- Dechallenge: positive/negative/not available
- Rechallenge: positive/negative/not available
- Alternative cause: probable/ruled out
- Risk factors: yes/no
- Previous information on the drug and adverse event: yes/no

Experts assessed each criterion and also made an overall causality assessment of "related" or "not related." Events were considered related if a relationship cannot be ruled out. They also provided the reasons for their evaluation. At the time of evaluation, the experts were not aware of the investigator's and sponsor's assessments.

Experts were CRO medical monitors. Their medical background included internal medicine, infectious diseases, pediatric and intensive care. None of them were medical oncologists, but they received trainings in different aspects of oncology and were medical monitors in various oncology clinical studies. Three experts (experts A, B, and C) had > 10 years of experience as monitors. Expert D had six months of experience. All four have solid experience in clinical practice and expert D has 20 years of experience as a clinical investigator.

Cohen's kappa agreement coefficient was used to assess agreement of each expert with the original reporting investigator. Contingency tables illustrating the agreement were also created. The results (near-zero values, CI covers zero in all cases) indicate that the investigator assessment is not related to that of any of the experts. This analysis was done for overall assessment only. Frequencies of concordant (same for all four experts) and discordant (split into 2 vs. 2 and 3 vs. 1 categories) evaluations were summarized for overall assessment, as well as for the individual Items. Three vs. one assessments were further analyzed to identify the expert who disagreed with the other three. Frequencies of being the disagreeing expert were summarized for the overall causality assessment, as well as for individual criteria. Chi-square test was then used to test the hypothesis that all the experts have equal chances of disagreeing with the three others.

Results

Adverse events were coded in accordance with MedDRA Version 18.0. The most common system-organ-classes (SOC) were respiratory, thoracic, and mediastinal disorders—11 (22%), and general disorders and administration site conditions—10 (20%). The proportion of all SOCs is presented in Table 1.

Distribution of Adverse Events

SOC	N (%)
Respiratory, thoracic and mediastinal disorders	11 (22%)
General disorders and administration site conditions	10 (20%)
Cardiac disorders	6 (12%)
Infections and infestations	5 (10%)
Gastrointestinal disorders	4 (8%)
Blood and lymphatic system disorders	3 (6%)
Vascular disorders	3 (6%)
Metabolic and nutrition disorders	2 (4%)
Psychiatric disorders	2 (4%)
Nervous system disorders	2 (4%)
Hepatobiliary disorders	2 (4%)

Source: Kosov

Table 1. The proportion of adverse events among all system-organ-classes (SOCs).

The disease under study—NSCLC—could explain this distribution of AEs, where the most frequent and expected adverse events are related to respiratory and cardiac systems. Another contributing factor is that we assessed serious AEs, which most likely are more clinically significant and, thus, more likely to involve vital organs and functions. The rate of agreement within the group of experts varied according to the criterion under evaluation (see Table 2 on facing page).

All four experts agreed on causality assessment in 32% of cases and, as expected, the pattern of assessment was different for the causality criteria. Maximal agreement was seen for expectedness (reaction previously reported) and risk factors. Interestingly, assessment of expectedness criterion was based on the data from the Investigator's Brochure, where all previously registered and expected AEs were enlisted, but, nevertheless, in 12% of cases assessment was not unanimous. Assessment of dechallenge and rechallenge was not informative and in the vast majority of cases was recorded as "not applicable." Only one AE occurred during infusion of the medication and in this case it was possible to assess a dechallenge effect, which was positive, according to all four experts.

There were several AEs where three experts were in agreement, while the fourth had a different opinion. We analyzed the pattern of such disagreement of one expert with three others on a specific AE (see Table 3 on page 46).

Statistically significant differences were seen in evaluation of time to onset, alternative cause, and overall causality assessment.

We did not analyze agreement between the experts and investigators in assessment of separate causality criteria, as only the overall causality assessment was available from the investigators. Overall agreement between all four ex-

perts and the investigators in assessment of AEs was 32% (16 cases); however, agreement was much higher for experts A, B, and C, with >10 years of experience in the capacity of medical monitor, at 70%-74%, while for expert D it was only 44% (see Table 4 on page 47). Based on the findings, Expert D seemed to be more liberal in attributing causality as likely related to study drug. This may partially be explained by a difference in perspective, since this expert has been a clinical investigator.

Causality assessments made by the sponsors concurred with those of the investigators in 48 cases out of 50 (96%). In two cases when it was different, the experts' assessment was the same as the sponsor's and in the other, two experts concurred with the sponsor and two with the investigator.

After unblinding of treatment assignments from placebo-controlled trials, it turned out that in four cases out of 20 (20%) where placebo had been given, the investigators assessed causality as "related." Interexpert agreement in evaluating placebo group also was not unanimous and AEs were assessed as "related" in 1 (expert A), 4 (expert B), 5 (expert C), and 14 (expert D) cases.

Discussion

More than 30 drugs have been recalled from the US market since the 1970s, some in use for several decades. According to the FDA, "A drug is removed from the market when its risks outweigh its benefits. A drug is usually taken off the market, because of safety issues that cannot be corrected, such as when it is discovered that the drug can cause serious side effects that were not known at the time of approval."[6] Darvocet (propoxyphene), an opioid pain reliever, was recalled in 2010 after being on the market for 55 years, due to serious cardiotoxicity; over 2,000 deaths were reported between 1981 and 1999.[7] Duract (bronfenac), a nonsteroidal anti-inflammatory drug, was withdrawn in 1998 after being on the market for a few months, due to significant hepatotoxicity; four deaths resulted and eight patients required liver transplants.[8] It seems evident that the more comprehensive the information about possible ADRs is obtained during clinical development, the more likely the drug will remain on the market. Thus a careful assessment of AEs and particularly causality are of great importance.

Methods used for assessment of causality can be grouped into three categories: expert judgement, probabilistic approaches, and algorithms or scales.[9] Despite numerous methods, there is still no "gold standard" and, to a large extent, assessment is based on physicians' evaluation. In clinical trials, a probabilistic approach is used—most frequently the WHO-UMC system and its modifications.[2] Early studies showed poor agreement between experts in assessment of causality of ADRs. Several assessment criteria are addressed in a "yes-no" fashion: timely relationship, alternative explanation, dechallenge, and rechallenge.

> **One of the key characteristics of every ADR is causal relationship, or causality—whether the event under question is obviously related to the study drug, or at least such relationship cannot be ruled out.**

There are six possible outcomes for causality assessments in the WHO-UMC system: certain, probable, possible, unlikely, unclassified, and unassessable. "Certain" has a unique requirement: the "event must be definitive pharmacologically or phenomenologically, i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon." An example is "grey baby syndrome," which is a rare but serious side effect that occurs in newborn infants (especially premature babies) following the intravenous administration of the antimicrobial chloramphenicol due to the lack of a hepatic enzyme to metabolize the drug. This criterion is applicable only in cases of already known, previously ob-

Assessment of Causality Criteria

EXPERT'S AGREEMENT	OVERALL	TIME TO ONSET	REACTION PREVIOUSLY REPORTED	ALTERNATIVE CAUSE	DeCHALLENGE	ReCHALLENGE	RISK FACTORS
All Agree	16 (32.0%)	16 (32.0%)	44 (88.0%)	31 (62.0%)	1 (2.0%)	NA	37 (74.0%)
One vs. Three	25 (50.0%)	27 (54.0%)	4 (8.0%)	15 (30.0%)	NA	NA	13 (26.0%)
Two vs. Two	9 (18.0%)	7 (14.0%)	2 (4.0%)	4 (8.0%)			

Source: Kosov

Table 2. The rate of agreement within the group of experts varied depending on the criterion under evaluation.

Expert Disagreement Measures

EXPERT	OVERALL	TIME TO ONSET	PREVIOUSLY REPORTED	ALTERNATIVE CAUSE	RISK FACTOR
A	0 (0.0%)	1 (3.7%)	0 (0.0%)	9 (60%)	4 (30.8%)
B	4 (16%)	3 (11.1%)	1 (25%)	2 (13.3%)	3 (23.1%)
C	1 (4.0%)	10 (37%)	3 (75%)	0 (0.0%)	1 (7.7%)
D	20 (80.0%)	13 (48.1%)	0 (0.0%)	4 (26.7%)	5 (38.5%)
p-value	<.001	0.002	0.112	0.008	0.442

Source: Kosov

Table 3. The frequency of one expert disagreeing with the other three experts.

served, specific reactions. Such knowledge is not common in clinical trials, especially at the early stages. However, certain types of reactions specific for a class of drugs could meet this criterion during a trial.

For regulatory purposes, the six WHO-UMC causality categories are collapsed into just two categories—related and not related. Certain, probable, and possible map to "related," and unlikely, unclassified, and unassessable make up "unrelated." There are certain difficulties in distinguishing between probable and possible and frequently investigators do not consider them. Accordingly, we decided to simplify the analysis and classify AEs as related or not-related. We also modified assessment criteria and added to traditional time to onset, dechallenge/rechallenge, and alternative cause—such criteria as risk factors and previous information on the drug. Evaluation of temporal relationship is based on a general assumption that it takes between five and six half-lives for a medication to be eliminated from the body; consequently, it is generally accepted that one can exclude a temporal relationship with a medication, if the time since the last administration is ≥ 5 x T1/2. However, this approach is frequently not observed in clinical practice and is a matter of approximation. Another limitation is possible variations of pharmacokinetic parameters, including half-life, due to pathologic conditions and drug-drug interactions. *Khan et al.* showed that patients with severe or acute respiratory disorders generally use multiple drugs and have increased susceptibility to ADRs.[10]

Positive dechallenge and rechallenge theoretically could be considered "a gold standard" of causality, but in practice their use is limited. Dechallenge could be mainly used for infusion reactions, when stopping drug may, or may not, lead to a quick resolution of clinical signs and symptoms. It is not useful when an ADR occurs some length of time after a drug administration—sometimes days or weeks. Dechallenge also may not be applicable in single-dose studies or long-lasting reactions, like hepatotoxicity or congenital anomalies. A rechallenge rarely occurs due to ethical concerns. An analysis of the performance of the CIOMS scale in the Spanish DILI (drug-induced liver injury) Registry showed that rechallenge data were absent in >95% of all cases.[11]

Positive dechallenge and rechallenge theoretically could be considered "a gold standard" of causality, but in practice their utility is very limited.

For drugs that are administered with a certain periodicity, repetition of the ADR after one of the subsequent administrations may reflect a positive rechallenge. At the same time, there are two main limitations: the incidence of even drug-related reactions is not 100%, thus if seen after one administration, the ADR will not necessarily repeat after the next one, and some drugs are given once weekly or even more rarely (e.g., chemotherapeutic medications) and this criterion could be assessed only retrospectively. In our study, only one ADR out of 50 was assessed for dechallenge and it was a psychiatric disorder that occurred during drug infusion and resolved after the drug was discontinued.

Under the category of "previous information on the drug and adverse experience," we meant information about the drug that was available at the time of the ADR. For experimental drugs, investigators receive this information from a periodically updated Investigator's Brochure. Another source of ADR-related information was providing investigators with individual case safety reports (ICSRs) delivered as MedWatch 3500A or CIOMS-I forms during the study conduct. However, these forms are being distributed for the events that have already been considered SUSARs (suspected unexpected serious adverse reactions). Those that were considered not related are not provided to investigators.

Interestingly, in 20% of patients who later appeared to receive placebo, causality was assessed as related by the investigators, and discordance between the experts was also high. We can theorize, that in placebo-controlled trials, evaluation of AEs should be made with more caution, as there

Expert-Investigator Agreement

	INVESTIGATOR ASSESSMENT			
EXPERT A ASSESSMENT	**N**	**Y**	**KAPPA**	**CI**
N	33 (66.0%)	8 (16.0%)		
Y	7 (14.0%)	2 (4.0%)		
Agreement			0.0260	[-.2590; 0.3110]
EXPERT B ASSESSMENT	**N**	**Y**	**KAPPA**	**CI**
N	36 (72.0%)	9 (18.0%)		
Y	4 (8.0%)	1 (2.0%)		
Agreement			-.0000	[-.2559; 0.2559]
EXPERT C ASSESSMENT	**N**	**Y**	**KAPPA**	**CI**
N	32 (64.0%)	7 (14.0%)		
Y	8 (16.0%)	3 (6.0%)		
Agreement			0.0964	[-.2015; 0.3943]
EXPERT D ASSESSMENT	**N**	**Y**	**KAPPA**	**CI**
N	14 (28.0%)	2 (4.0%)		
Y	26 (52.0%)	8 (16.0%)		
Agreement			0.0789	[-.0790; 0.2369]

Source: Kosov

Table 4. Respective agreements between all four experts and clinical investigators in assessment of overall causality criteria.

is a chance that a patient was receiving a placebo instead of an active drug, and unblinded safety data received during the study can't adequately characterize the safety profile of a drug.

Divergences between experts in ADRs causality assessment have been reported previously. A*rimone et al.* compared judgment of five experts using VAS score and confirmed marked interexpert disagreement (kappa=0.20).[12] In the study of K*arch et al.*, agreement between three clinical pharmacologists in assessing ADRs was 50% and complete agreement between them and the treating physicians was slightly lower, in 47% of cases.[13] A*rimone et al.* reported the rate of agreement between experts with kappa indices of the causality criteria ranged from 0.12 to 0.38.[14] In the study of L*ouik et al.*, four experts rated 50 case reports first using only general guidelines and showed poor agreement.[15] Influence of subjective judgement was shown by M*iremont et al.*, who compared physicians' opinion with the scores obtained by the causality assessment method.[16] They showed that physicians more frequently assessed causality as "likely" and "very likely" related and complete agreement between physicians and causality assessment method was achieved in only 6% of cases. Previously, we showed discordance in causality assessment between investigators and a retrospective evaluation with Naranjo algorithm.[17]

In our present study, an expert with great experience as investigator and less experience as medical monitor, showed

> **Assessment of AEs' causality is subjective and influenced by individual judgement, and, thus, does not reflect a safety profile of the drug.**

significantly lower agreement with investigators than the three other experts did, in whom the rate of agreement was 70%-74%. The actual agreement is illustrated by kappa scores (Table 4), and they are all low, meaning investigators and experts are probably using different approaches. The high percentage of concordant records does not indicate agreement, but it indicates that both the expert and the investigator are considering the majority of events as "related." The criteria of time to onset and alternative cause of the event were the most frequent reasons for disagreement between the experts. The overall agreement on causality assessment was low, at 32%.

Consensus between experts is difficult to obtain when evaluations are made based on personal judgements of unspecified criteria. Developing methods of standardized assessments could solve this problem. In an attempt to minimize the subjective component, several algorithms for evaluation of ADR causality have been proposed: the Naranjo criteria, the Kramer algorithm, the Jones' algorithm, the Yale algorithm, and several others.[18] However, existing algorithms also show significant disagreement in assessing causality of the same ADRs with the most frequently seen discordance in evaluating timing of event, dechallenge, and alternative cause.[19] The most frequently used causality assessment algorithm is the Naranjo tool, which is simple and convenient, but its validity has been variably assessed; some studies demonstrated good agreement,[20] while others questioned its reliability.[9,21]

Considering the low validity and reproducibility of general methods for assessing ADRs, several groups attempted to develop algorithms for evaluating certain types of ADRs. Several algorithms have been suggested

for causality assessment of DILI: Maria and Victorino, DDW-J, and CIOMS-RUCAM (Roussel Uclaf Causality Assessment Method).[22,23] At the same time, causality assessment in different pathological conditions (e.g., lung cancer and Crohn's disease) is evaluated using the same general approaches. Both patient characteristics (e.g., age, comorbidities, and concomitant treatment) and disease characteristics (e.g., tumor burden, specific laboratory parameters) may influence incidence and severity of ADRs. At present, none of the existing causality assessment tools takes any of them into account.

Conclusion

Our study confirmed that the overall agreement between investigators and drug safety experts is low. Disagreements between experts may be due to different clinical background, perspective, and expertise. At the same time, we observed disagreement in assessment of such objective criterion as previously reported reactions. Our findings concluded that assessment of AEs' causality is subjective and influenced by individual judgement of investigator/expert, and, thus, does not reflect a safety profile of the drug. It is reasonable that safety assessments are made on an aggregate data.

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It's Time to Transform Clinical Trials Operations

Business leaders should have an accurate, up-to-date picture of clinical trials in progress, with full visibility into the workflow.

Jennifer Goldsmith
Senior Vice President, Veeva Vault, Veeva Systems

Managing clinical trials is an arduous process. There are many moving parts across a growing, complex ecosystem of internal and external stakeholders. Technology has alleviated some of the pain, but it has also created unintended consequences for operations teams and business leaders. Point solutions for study startup, electronic trial master files (eTMFs), and clinical trials management have improved certain areas, but the clinical operations environment remains highly fragmented.

It's time to move beyond a point-solution approach if a seamless, end-to-end clinical operations environment is ever going to be a reality. The challenge is that operations teams support different areas of the trial process, and naturally have their own processes and requirements. So it makes sense that each group implements discrete solutions to address their specific needs but they also need to access a lot of the same data, documents, and information. Yet each of their disparate systems is its own island, making it difficult for groups to share content and data across workflows and business processes.

The simple practice of conveying the study or site information can become difficult as study IDs, site IDs, investigator names, and more are all entered into one system and then duplicated in other clinical operations systems. This creates the potential for misinformation and transcribing errors, plus forces complex integration codes that must be maintained. And then there are the crucial milestones that must be documented but require information stored across multiple places. These milestones may be related to study startup package completion and draw from the clinical trial management system (CTMS) and eTMF. Since each group has its own system, trying to access the same information is cumbersome. Teams often waste hours trying to get their hands on the right information amidst a sea of documentation.

The clinical trials process is just as painful for business leaders seeking a complete, up-to-date picture of the status of a trial or portfolio of studies. No singular view exists because content and data live in different systems. Information has to be manually pieced together in spreadsheets, creating a picture that is incomplete. This makes it difficult for country leaders to make comparisons across local studies to streamline processes for study startup, ensure compliance with their portion of the TMF, or re-use documents in subsequent trials.

Point solutions such as eTMF and study startup software have enhanced visibility, collection, tracking, and management of content and data. They have provided measurable improvements to many aspects of the trials process, but the pieces are still not connected together to create a truly end-to-end operations environment. According to a new study by CenterWatch, in fact, sites worldwide are being inundated with a growing number of technology solutions that are difficult to use and are not compatible. On average, the typical site is working with 12 different systems to collect clinical research data.

Something different is needed—an underlying technology platform and set of applications that are natively built and designed to manage the full clinical trial process. What's needed now is a platform that would further streamline studies and give operations groups and business leaders everything they need at their fingertips to eliminate the manual handoffs and data collection. The task of sharing study IDs or other basics should be easy. But it's not. Business leaders should have an accurate, up-to-date picture of clinical trials in progress, with full visibility into how their staff is managing the workflow, data, and business processes. And they don't … at least, not yet.

We help you take care of the hard part, so she can get on with the hardest part.

Fighting cancer will be one of the hardest things she'll do. But getting the medicine she needs from your company, to her bedside, can sometimes seem just as challenging. Idis have more experience implementing Managed Access Programs than anyone else. It means we can overcome all the early access barriers quickly, ethically, and safely to get Ella what she needs.

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PATIENT-CENTERED RESEARCH

AT MAPI, PATIENTS ARE AT THE HEART OF EVERYTHING WE DO

Mapi Group believes that listening to patients is the most crucial element in improving world health.

The wide range of services we offer helps ensure that the voice of the patient is heard throughout the development process. Our commitment to patients has established Mapi Group as the industry leader and chief innovator of patient-centered research. For over 40 years, the Life Science industry has relied on Mapi experts for guidance on integrating the patient's voice into health research.

- Real World Evidence
- Real World Strategy & Analytics
- Language Services
- Strategic Regulatory Services
- Mapi Research Trust

Upcoming Webinars

Gastrointestinal Quality of Life Questionnaire (GIQLI)
September 7

Neuropathic Pain Symptom Inventory (NPSI) for Clinical Research Assessment of Patient Pain
September 15

Hybrid Retrospective & Prospective Study Designs
September 19

Risk Management Plans – Europe and Beyond
September 22

How to Prepare Development Safety Update Reports
September 27

Cuba's Regulatory Landscape
September 28

Advanced Evidence Synthesis Methods
October 4

Evidence Synthesis & Evidence Generation to Accelerate Market Adoption
October 17

Inhaled Corticosteroids Questionnaire (ICQ)
October 19

Periodic Benefit Risk Evaluation Reports
October 25

Visit mapigroup.com/webinars to register

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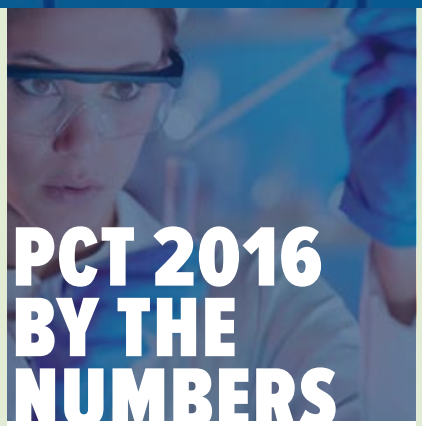
INNOVATION

Everyone talks about it. But we all know creating a culture of innovation in Life Sciences is more than just introducing new ideas, devices, or methods. So what does it mean, and more importantly, how do you do it? PCT 2016, takes a deep dive beyond the keynotes into **Innovating Processes and Technologies** that provide real enhancements in processes, tools, and systems that are unique in design, approach, and concept. You know, real innovation. Not just the word.

- Build innovative partnerships between people and technology
- Utilize technology to transform global health
- Foster R&D innovation with process improvements for planning, implementing, and reporting clinical trials
- Process innovation and lessons learned from reducing clinical trial timelines
- Explore the use of wearables, mobile apps, digital tools and other technologies in clinical trials

Learn more about these sessions and download the complete agenda at **www.clinicaltrialspartnerships.com**



PCT 2016 BY THE NUMBERS

50+
Case Studies, Presentations, and Panels

1,100
Clinical Trials Stakeholders

100+
Influential Thought Leaders and Expert Speakers

25
Years in the Making

60+
Technologies and Solutions Providers

PATIENT CENTRICITY

Patients are the heart of Clinical Trials. And as every minute passes, clinical professionals and advocacy groups step up efforts to integrate the "patient" into everything you do–optimize trial design, increase patient enrollment, improve engagement, and more. PCT 2016 brings the patient clearer into focus through successful patient-centered approaches in clinical trials so you can do better:

- Patient benefits of mobile technologies in trials
- Traditional and non-traditional trial design to optimize enrollment, engagement and overall success
- Successful recruitment strategies for trials with constricted patient criteria
- Managing trials and patient recruitment in emerging markets
- Cultural and socioeconomic considerations that impact trial execution
- Data transparency and the connection to patient enrollment/ engagement in trials
- Minimizing risk in data sharing

PARTNERSHIPS IN CLINICAL TRIALS US IS NOW PART OF THE ALL NEW BIOTECH WEEK BOSTON (BWB)

BWB brings together four world-class conferences, in the beating heart of the biotech industry, that build a bridge from the research bench to the patient's bedside to expedite the approval and delivery of life-saving therapeutics. Visit www.biotechweekboston.com to find out more.

All BWB elements are noted with a B and are part of your PCT registration pass at no additional charge.

Partnerships in Clinical Trials US

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Boston, MA

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Co-Founder, Apple Computer Inc.
Innovation & Customer Centricity

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PREPARE YOURSELF TO BE WOWED AND INSPIRED

From innovation to finance to big data and back, PCT Keynotes feature thought leaders, luminaries, and visionaries you must hear and apply the nuggets of insight and knowledge to your daily clinical R&D world.

Innovation in Clinical R&D: Finding a Cure for Alzheimer's

MARTIN TOLAR
MD, PhD – Founder, President & CEO, Alzheon, Inc.

Innovating the Clinical R&D Landscape with Technology

KAILASH SWARNA
Associate Partner, IBM Watson Health Group

Aspiring to Work Together with Sites for Patients

PETER RONCO
VP, Global Clinical Operations (GCO), R&D, Bristol-Myers Squibb

Looking for Sustainable Business Models in Pharma: The Impact of M&A and other Risk-Sharing Trends on Clinical Development

JOSEPH A. DIMASI
PhD., Director, Economic Analysis, Tufts University

Outside Industry Insight Panel – Big Data

SUMIT SEHGAL
CTO Healthcare Security, Intel

Outside Industry Insight Panel - Innovation

JACK SABA
Co-Founder & Managing Partner, Day One Investments

Learn more and download the complete agenda at **www.clinicaltrialspartnerships.com**

JOIN US IN THE ALL-NEW PCT LOFT, WHERE YOU CAN INNOVATE CLINICAL TRIAL DESIGN & OPERATIONS, AND CULTIVATE THE RIGHT RELATIONSHIPS

You'll find a mix of what's new and necessary at PCT 2016 in interactive formats that compel honest dialogue, thought-provoking commentary, and strategic discussion—all yielding the actionable takeaways you need to get the job done!

- **NEW!** Outside-Industry Keynotes on outsourcing, data analytics, customer service, and innovation for fresh insights and best practices to apply to your trials
- **NEW!** Spotlight Presentation–R&D Challenges in Finding a Cure: Lessons Learned from Running a Clinical Trial for the Zika
- **NEW!** In-Depth Workshops including The Future of Clinical Trials: Rethinking the R&D Clinical Process
- **NEW!** Innovation Presentations–Rapid fire pitches on cutting-edge innovation and tech to make your trials more cost effective and efficient, 10 minutes at a time
- **NEW!** Partnering Discussions–Find like-minded peers and technologists during focused, niche roundtable discussions to help you overcome specific challenges in your trials
- **BACK BY POPULAR DEMAND!** Wall Street Keynote–Looking for Sustainable Business Models in Pharma: The Impact of M&A and other Risk-Sharing Trends on Clinical Development

Get the real deal at PCT 2016. Download the full agenda and register at:
www.clinicaltrialspartnerships.com

THERE'S NO SUBSTITUTION FOR "FACE TIME" AND NETWORKING

Having a coffee. Walking the hall. Sitting in a session. Sampling an hors d'oeuvre. Grabbing a drink, or two. These are all points at which you can—and will—chat it up with your colleagues and peers to find a new partner, rekindle business relationships, and make a new friend. And this year, PCT upped the ante.

DON FELDER

SUSAN WINDHAM-BANNISTER

PCT LOFT & BAR All 3 Days Because Why Not? • 2nd Floor

Ⓑ **CELEBRATION OF SCIENCE** Oct 5 • 6pm • BWB Hall

Ⓑ **WOMEN'S LEADERSHIP SYMPOSIUM & DINNER**
Featuring Susan Windham-Bannister of Biomedical Growth Strategies and formerly of Massachusetts Life Sciences Center
Oct 5 • 6pm • BCEC *(separate registration required)*

Ⓑ **PARTY IN THE PARK** Featuring Don Felder, formerly of the Eagles
Oct 6 • 6pm • The Lawn on D

See the full social calendar at **www.clinicaltrialspartnerships.com**

ONE FOR ALL AND ALL FOR ONE

Whether you hail from a small tech start-up, a growing biotech, or a specialized medical device company, you need tailored content that directly addresses your unique needs and allow you to immediately apply it to your trial operations and research. PCT 2016 delivers on this and more. Not only will you find sessions and thought leaders that speak directly to your company type, but you'll also find concentrated thinking on innovation and patient-centricity woven throughout the three days of the agenda.

Because if it's not relevant to you or about the patient, why bother?

SMALL-MID SIZED PHARMA

FOCUS DAY WORKSHOP:
You Are Your Vendor's Keeper: Effectively Managing Vendor Oversight
John Shillingford, PhD., Independent Consultant, **Pharmaceutical Training International (PTI)**

Get curated, well-rounded perspectives and insights from Small-Mid Size Pharma Companies in these other sessions across the three days:

- ***Innovative Investigator Meetings – How Technology Can Engage an Audience***
- ***A Risk-Based Approach to Quality & Compliance***
- ***If It Wasn't Validated, It Didn't Happen: A Practical Guide to Embracing a Compliant SDLC***
- ***The State of Sponsor-CRO Strategic Partnerships and How the Industry Has Evolved in the Past Five Years***
- ***Overcoming Difficulties in Running a Global Trial***

BIOTECH

Keeping up with Biotech in Immuno-Oncology
Nicole Chieffo, Global Operations Head, Oncology, **Johnson & Johnson**

A Risk-Based Approach to Quality & Compliance
Michael Brinkley, Vice President, Quality and Analytical, **Endocyte**

Biotech Perspective on Overcoming Difficulties in Running a Global Trials
Raj Malik, MD, Chief Medical Officer, **G1 Therapeutics**

PCT Focus Workshop Emerging Markets: Deep Dive: Latin America & Africa
Gaurav Puppalwar, MD, Head Medical Affairs, **Wockhardt**

MEDICAL DEVICE

Human Factors Trial Design and Management
Tina Rees, Ph.D., Senior Research Scientist-Human Factors, **Eli Lilly and Company**

Addressing the Challenges in Including Investigational Devices in Clinical
Jennal Johnson, Principal Research Scientist, Diabetes, Global Development, **Eli Lilly and Company**

A Closer Look at the Emerging Medical Device Market in Asia
Dr. Timothy Low, CEO, **Farrer Park Hospital**, Singapore; former Vice President, Medical Affairs, Asia Pacific, **Covidien, a Medtronic company**

AGENDA AT-A-GLANCE

SESSION LEGEND: KEYNOTE | INNOVATION | PATIENT CENTRICITY | BIOTECH WEEK BOSTON

FOCUS DAY WORKSHOPS WEDNESDAY, OCTOBER 5

	You Are Your Vendor's Keeper – Effectively Managing Vendor Oversight	Patient Recruitment & Identification Bootcamp	Emerging Markets	NEW! The Future of Clinical Trials: Rethinking the R&D Clinical Process
9:00 A.M. **PART 1**	Implementing an Effective Vendor Management and Governance Structure	Aligning Protocols with Targeted Patient Populations	Deep Dive: APAC Region	Eliminating Division in Clinical R&D & Trial Design
11:00 A.M. **PART 2**	Examining Vendor Management Case Studies & Approaches	Leveraging Technology & Innovative Recruitment Strategies	Deep Dive: Latin America & Africa	Radically Changing Clinical Trial Processes to Streamline R&D & Lower Costs
2:00 P.M. **PART 3**	Vendor Management and Oversight in Emerging Economies	Tracking Recruitment Efforts for Strategic Insights	Deep Dive: Eastern Europe	Examining Real World Examples & Methodological Thinking in Trials

4:30 P.M.	*BWB Opening Night: Celebration Of Science*
7:00 P.M.	*BPI Magazine Awards Reception and Dinner* (Separate Registration required)
	Women's Leadership Symposium and Dinner (Separate Registration required)

MAIN CONFERENCE THURSDAY, OCTOBER 6

7:00 A.M.	*Breakfast and Morning Coffee*
	PARTNERSHIP BREAKFAST PRESENTATIONS: The Expectations and Realities of Clinical Trial Evolution – Digital to EHR Data – Greg Sweatt, Sr VP, Life Sciences, **ePatientFinder**
	INNOVATING THE CLINICAL DEVELOPMENT SPACE
8:15 A.M.	**OPENING PCT KEYNOTE:** Innovation in Clinical R&D: Finding a Cure for Alzheimer's – Martin Tolar, MD, PhD – Founder, President & CEO, **Alzheon, Inc.**
8:45 A.M.	**KEYNOTE:** Innovating the Clinical R&D Landscape with Technology – Kailash Swarna, Associate Partner, **IBM Watson Health Group**
9:30 A.M.	**BWB KEYNOTE:** Emerging Global Health Issues
10:15 A.M.	*Refreshment Break*
11:00 A.M.	**UNLEASHING INNOVATION:** A Case Study on Wearables – **Medidata Executive TBA**
11:35 A.M.	**NEW! SPOTLIGHT PRESENTATION:** Rapid Response R&D in Disease Outbreaks: Our Experience with Ebola and Zika and How this could be Applied to all Clinical Trials

*Schedule subject to change

12:10 P.M.	**NEW! OUTSIDE INDUSTRY INSIGHT PANEL PERSPECTIVES**					
	Innovation Perspective Jack Saba, Co-Founder & Managing Partner, **Day One Investments**	**Outsourcing Perspective** Executive, TBA	**Big Data Perspective** Sumit Sehgal, CTO Healthcare Security, **Intel**	**Customer Service Perspective** Executive, TBA		
1:15 P.M.	**NEW! PARTNERING FORUM DISCUSSIONS**					
	Site Alliances as a Competitive Advantage for CROs	Trending Now: Is #Mobile Health Just a Fad?	Patient Perspectives in Trial Design	The Role of QA in CRO Selection	The Future of Biologics in Clinical Trials	Partnering in Medical Devices: Best Practices and Lessons Learned
	Transforming Partnerships into Strategic Alliances: Strategic Outsourcing & Procurement	**Data & Informatics in Clinical Development**	**Innovating the Clinical Partnerships Landscape with Disruptive Technologies**		**Patient Centricity: Patient Recruitment & Engagement**	
2:35 P.M.	**DEBRIEF PANEL:** Applying "Outside Industry" Best Practices in Outsourcing & Procurement to Clinical Development	**DEBRIEF PANEL:** Applying "Outside Industry" Best Practices in Data & Informatics to Clinical Development	**KEYNOTE:** Innovating with Disruptive Technology		**KEYNOTE:** **Aspiring to Work Together with Sites for Patients**	
3:30 P.M.	**PANEL DISCUSSION:** Optimizing Collaboration Effectiveness in Alliance Partnerships: Opportunities & Progress	Using Clinical Data to Support Strategic Analysis	3:00 P.M.	**DEBRIEF PANEL:** Applying "Outside Industry" Best Practices in Innovation to Clinical Development	3:00 P.M.	**PANEL DISCUSSION:** How to Incorporate Patient-Insights into a Drug Development Program
4:05 P.M.	Keeping up with Biotech in Immuno-Oncology	Integrating Systems and Tools used During Clinical Trials	3:55 P.M.	Innovative Investigator Meetings – How Technology Can Engage an Audience	3:55 P.M.	Transparency and the Road to Patient Engagement
4:30 P.M.	*Refreshment Break in the PCT Loft Bar*					
5:00 P.M.	**BWB PANEL:** Health and the Election: The Implications of Promises and Policy on Pricing and other Issues that Matter– Moderated by STAT					
6:15 P.M.	*Party in the Park at the Lawn on D*					

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MAIN CONFERENCE FRIDAY, OCTOBER 7

7:00 A.M.	*Morning Coffee and Registration*			
THE FUTURE OF CLINICAL DEVELOPMENT PARTNERSHIPS: FINANCIAL IMPLICATIONS				
8:15 A.M.	**BACK BY POPULAR DEMAND! WALLSTREET KEYNOTE:** The Impact of M&A and other Risk-Sharing Trends on Clinical Development – Joseph A. DiMasi, PhD., Director, Economic Analysis, **Tufts University**			
9:15 A.M.	**BWB KEYNOTE:** Innovation & Customer Centricity – Steve Wozniak, Co-founder, **Apple Computer Inc**			
10:15 A.M	**NEW! BWB THEATER ZONE:** Clinical Innovation Focus Sessions A series of 10-minute rapid fire company presentations solely focused on innovating processes and technologies			
THE FUTURE OF CLINICAL DEVELOPMENT PARTNERSHIPS: ACCELERATION, COST & QUALITY				
	Risk-Based Approaches in Clinical Trials	**Focus on Regulation**	**Operational Excellence & Optimization in Trial Design/ Management**	**The Global Clinical Trials Community**
11:10 A.M.	A Risk-Based Approach to Quality & Compliance	If It Wasn't Validated, It Didn't Happen: A Practical Guide to Embracing a Compliant SDLC	**CASE STUDY:** Partnering with Payers	A Closer Look at the Emerging Medical Device Market in Asia
11:50 A.M.	Update on Risk-Based Monitoring: Years Later Where Are We Now?	The Keys to Success in for an FDA Audit	Human Factors Trial Design and Management	Little Known facts about Sourcing Comparators from RoW Markets and Associated Cost Savings
12:30 P.M.	Redefining Oversight in Strategic Partnerships – A Case Study of UCB's Implementation of a Risk-Based Approach to Sponsor Oversight in a Fully Outsourced Study	Regulatory Oversight and Vendor Relationships	Addressing the Challenges in Including Investigational Devices in Clinical	**PANEL DISCUSSION:** Overcoming Difficulties in Running a Global Trial
1:15 P.M	**PCT LUNCHEON KEYNOTE:** AVOCA Spotlight Presentation: The State of Sponsor-CRO Strategic Partnerships and How the Industry Has Evolved in the Past Five Years			
2:00 P.M	**PCT LUNCHEON DEBRIEF:** Aligning Around a Common Goal: Working Together to Transform the Industry for the Better			
	Small - Mid Size Pharma Perspective- Mitchell Katz, Executive Director, Medical Research Operations, **Purdue Pharma L.P.**	Med Device Perspective - Executive TBA	Biotech Perspective – Executive TBA	Clinical Specimen/ Lab Perspective- Brenda Yanak, Precision Medicine Lead, Clinical Innovation & BPO, Global Specimen Management, **Pfizer**	Clinical Trial Technology Perspective- Shree Kalluri, Founder & CEO, **Nimblify**
2:45 P.M.	*Closing Remarks, Conference Concludes*			

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- Access PCT Loft & Bar on the 2nd Floor and Clinical Café in the BWB Hall
- All Networking Breaks and Exhibits in the BWB Hall
- All Keynotes in the BWB Theatre, including Steve Wozniak
- Access to all submitted PCT Speaker Presentations following event

PCT 3-DAY PASS OCTOBER 5-7	**SAVE UP TO $300** by 8/12/2016	**STANDARD** (After 8/13/16)
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NOTE: The PCT 3-Day Pass grants access only to all PCT-only sessions, general sessions/keynotes, and exhibits and activities on the Shared Exhibit Hall Floor. It does not provide access to co-located events.

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