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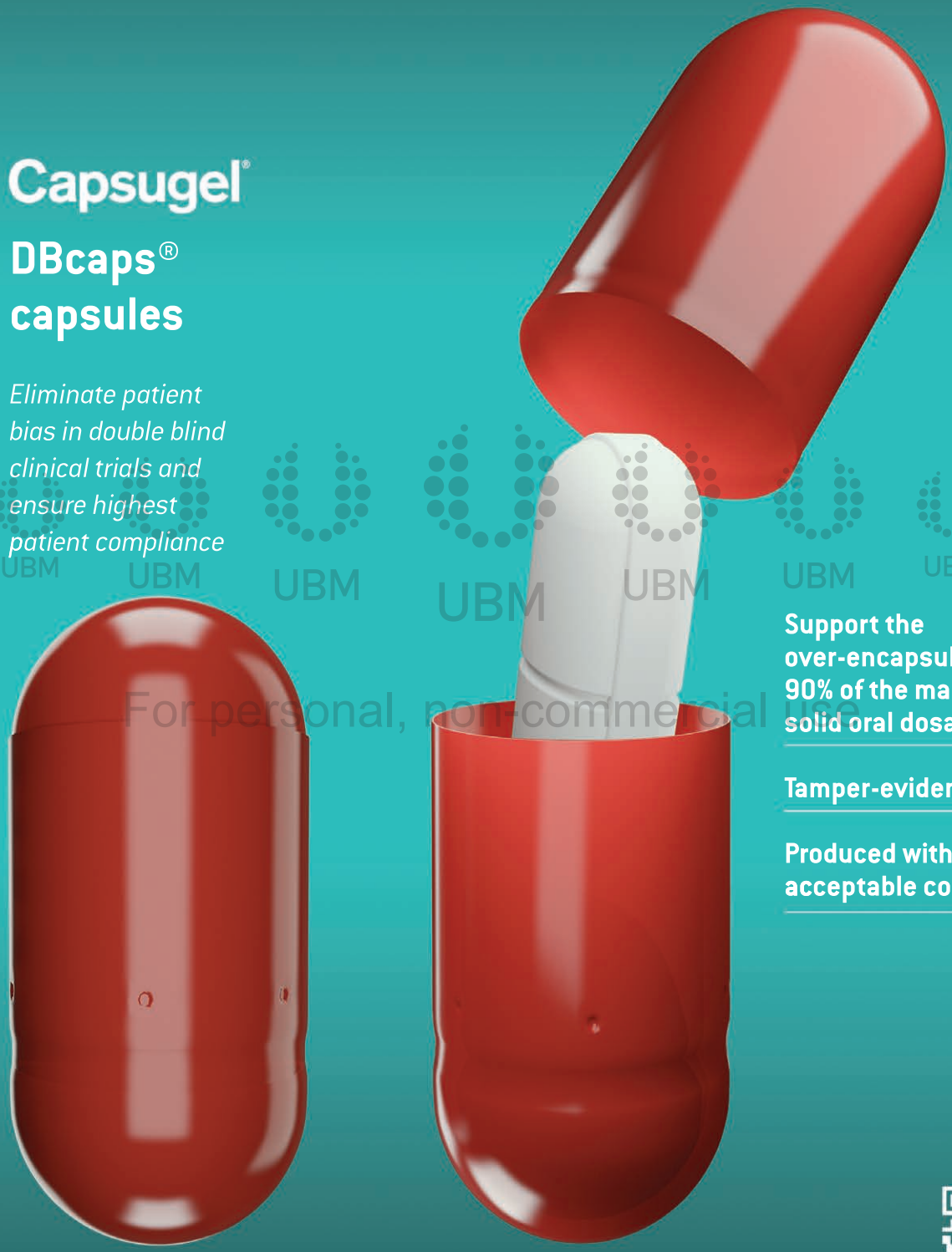

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Do As I Say, And As I Do

LISA HENDERSON
Editor-in-Chief

What is more tiring for anyone in this industry to hear? Is it the most oft-quoted statistic from the Tufts Center for the Study of Drug Development that the average cost of getting a drug developed through to marketing approval is $2.87 billion; or the blaming of the FDA? Or is it that FDA is the major hurdle to trying anything new in clinical trials? That the fear industry has of doing something differently in a clinical trial is that the agency will reject the data and, ultimately, the drug. It's clear the costs and industry practices behind clinical trials are not escaping the FDA, and they aren't pleased.

For the FDA's sake, let's put aside the argument that many clinical trials fail in Phase III before they even see the light of submission and face that FDA scrutiny. Let's also reject the notion that FDA is unwilling to work with pharma. The agency is more than willing to meet with sponsors very early on in their clinical trial planning processes to discuss options. These formal meetings also have their own guidance, bit.ly/2RSZ5HS, so it's not as if FDA is shutting everyone out of any potential discussions.

CDER and the FDA have backed up their support of basket trials, master protocols, and more collaborative types of trials by initiating for comment on Oct. 1 the draft guidance, "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics."

FDA also put forth for comment its draft guidance, intending to replace one from 2010, "Adaptive Designs for Clinical Trials of Drugs and Biologics," which provides direction on "the basic principles for designing, conducting, and reporting the results from an adaptive clinical trial."

It looks as if FDA supports changes in trial designs—as it has for the past eight years—to promote more efficient and timely review of results for drugs being tested in clinical trials. However, the FDA estimates that 40 sponsors will submit 240 plans for trials utilizing an adaptive design, and only 15 will prepare and submit to FDA 20 marketing applications that rely on an adaptive design trial.

In another article from Bloomberg Law, bit.ly/2FU51Zf, FDA Commissioner Scott Gottlieb hinted that CROs may need to reflect on their own processes that may be unnecessarily bloating drug development costs without adding value. In the same article, attorney Mark Barnes at Ropes & Gray pointed to monitoring activities as one of those processes. While he acknowledged that monitoring could be more risk-based, he then blamed the FDA, saying, "this goal of perfection in trial monitoring is a product of the FDA's own expectations of monitoring." No matter that FDA's guidance on the topic, "Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring," or its complementary partner, "Electronic Source Data in Clinical Investigations," have been available for five full years—since August and September of 2013, respectively.

From clinical trials to the commercial, FDA (and HHS), as well as smaller biopharma, are quickly tiring of these shenanigans. If you aren't part of the solution, you are going to be considered the problem. Being part of the solution isn't just lip service, it's putting that information out there transparently for everyone to measure and make decisions.

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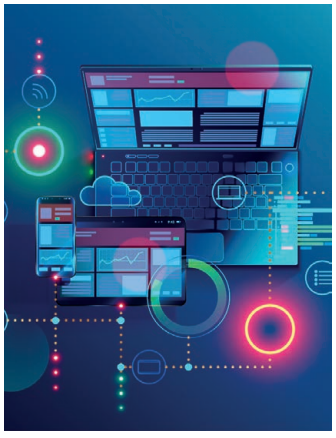

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WASHINGTON REPORT

FDA CLARIFIES RESEARCH POLICIES TO FACILITATE NEW DRUG DEVELOPMENT

This past year brought kudos to the biopharmaceutical research community, as manufacturers tested, and FDA approved, multiple innovative medical products, including important new cancer treatments, vaccines, cellular and gene therapies, and complex generics and biosimilars. Such advances have benefited from FDA efforts to streamline clinical testing methods, clarify regulatory policies, and accelerate application reviews to speed new therapies to market. FDA Commissioner Scott Gottlieb has emphasized the need to moderate the cost and time for developing new medicines to help bring down drug costs and spending. This objective has fueled agency efforts to update research policies, issue more draft and final guidances on investigative strategies, and to meet more often with sponsors and with stakeholders to advance development programs.

One visible result is a wave of new guidances outlining recommended approaches for testing certain types of drugs and for collecting research data. Recent draft guidances from the Center for Drug Evaluation and Research (CDER), for example, discuss endpoints for prostate cancer studies, meta-analyses for evaluating drug safety, methods for developing drugs to treat chronic hepatitis B, and use of certain markers in assessing metabolic malignancies (new CDER guidances listed at bit.ly/2r6AZam). There are advisories on using master protocols to expedite development of oncology therapies, on adaptive clinical trial designs, and on clinical pharmacology and toxicology issues. A recent listing of surrogate endpoints under development aims to help sponsors identify what markers might be useful in future R&D programs.

FDA also has held numerous public workshops and meetings to discuss models and approaches for advancing medical product development and to clarify regulatory procedures and policies (see bit.ly/2TTSDeT). Training courses help advance the expertise of clinical investigators, and patients continue to provide valuable perspectives on developing innovative treatments to agency experts and advisory committees. A recent advisory committee examined whether FDA should require cardiovascular outcomes trials in developing new diabetes treatments. And agency experts discussed the qualification of biomarkers, animal models, and clinical outcome assessments at a December public meeting.

A main challenge for sponsors is to achieve timely enrollment in clinical trials of sufficient numbers of qualifying patients. FDA is assessing study inclusion and exclusion criteria to identify barriers to increased diversity in study populations, including women and elderly patients. One recent guidance advises on enrolling adolescents in adult studies as part of efforts to include more under-represented patients in trials. And to reduce the complexity of research requirements, FDA recently proposed to limit informed consent requirements for studies that involve minimal risk to participants, as determined by institutional review boards.

To expedite the review of applications for cutting-edge therapies, the agency launched a pilot for real-time review of oncology drugs (see bit.ly/2TTSDeT). This allows early assessment of safety and efficacy data before the complete application is filed, as part of efforts to speed highly promising treatments for serious conditions more quickly to patients. CDER director Janet Woodcock hopes to expand the real-time review model to new treatments for additional serious conditions, and eventually to all new drug applications.

Further efficiencies are the goal of a reorganization of CDER's Office of New Drugs (OND), which aims to be finalized in another year (see bit.ly/2KE7fug). The new OND will have more offices and divisions able to oversee more similar therapeutics that raise common research issues and can be managed more efficiently. Project management and policy staffs will move from review divisions to central OND offices with the aim of being more flexible and ensuring greater consistency in review decisions for all drug classes.

— Jill Wechsler

FDA NEWS NOTES

The FDA recently released the following industry guidance documents:

11/13/18: Nonmetastatic, Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials (draft)

11/06/18: Hypertension: Developing Fixed-Dose Combination Drugs for Treatment

11/06/18: Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry (draft)

11/06/18: Hypertension: Developing Fixed-Dose Combination Drugs for Treatment Guidance for Industry

11/01/18: Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment (draft)

The following committee meetings were scheduled for December:

- Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement ***Dec. 4***
- Science Advisory Boardo NCTR Meeting Announcement ***Dec. 4***

EU REPORT

IT'S NOT THE TIME TO RELAX ON PEDIATRIC MEDICINES R&D

There are dangers in complacency. It is just over a year ago that the European Union published a self-congratulatory report on its progress in promoting the development of medicines for children. At the time, that move provoked some skeptical response; for instance, "European Union gives itself top marks for its pediatric medicines regulation" (see bit.ly/2G0FFJp). But a year on, a much more critical view of the situation has emerged among European pediatricians, drug developers, and—above all—parents of children with unmet needs. The European Forum for Good Clinical Practice teamed up with the Drug Information Association to mount a two-day review of the state of play in Brussels at the end of October, and their conclusions were far less favorable than the EU's own assessment of its achievements.

Absent treatments

Patient advocates, industry, and physicians spelled out the failings they were conscious of. While cancer remains the biggest killer of children by disease, in the 10 years from 2007, only two new cancer drugs were approved for children, compared to more than 50 for adults, pointed out Chris Copland, a prominent UK patient representative. He added that brentuximab vedotin had been approved for Hodgkin's lymphoma in adults in 2012; trials for pediatric use were still ongoing in 2016.

Regret tempered patient groups' satisfaction at access—at last—to a treatment for spinal muscular atrophy, because of the long delay and the still-limited access. The causative gene was identified in 1995, but the first product, Biogen's Spinraza, was authorized only in 2017, available only in 2018, and then only in a handful of countries for a handful of patients—less than a tenth of the estimated 20,000 patients in Europe.

Only two drugs are approved anywhere in the world for Duchenne muscular dystrophy, and only one in the EU—Translarna. And that is available only subject to strict limitations and tight conditions, as well as significant delays in securing treatment, even in prosperous European countries.

Absent infrastructure

Christina Bucci-Rechtweg, global head of pediatric and maternal health policy at Novartis, presented a formidable list of obstacles to access to new pediatric medicines and indications. Pediatric research infrastructures are not adequate, and research opportunities are missed. The consequences are gaps in pediatric-specific innovation, in treatment alternatives to high cost new pediatric innovations, and in inadequate supply of age-appropriate formulations.

Marie-Yvonne Douste-Blazy of Servier offered some potential solutions from the point of view of a company. An inventory of disease-based unmet pediatric needs could serve as a common basis for strategic decision-making among industry, regulators, epidemiologists, patient groups, and pediatrics networks, she proposed, particularly if it indicated clearly for each need what research was ongoing.

Absent reimbursement

But another of her priorities was to speed access to innovative drugs, reflecting the widely-supported view at the meeting from industry executives and patients that reluctance to reimburse innovations among Europe's health insurance systems was another hurdle. Other industry executives spoke of "non-prioritization of pediatrics in payment structures."

The omnipresent issue of money does indeed underlie much of the difficulty, conceded Evert Jan van Lente, director of EU affairs for the German health insurers association, AOK. But he did not consider that payers were the real obstacle, and nor did he see that tinkering with the system by adjusting incentives would be a sufficient solution. "Extending supplementary protection certificates or market exclusivity are just not appropriate mechanisms," he said. His starting point was that the return on investment from new pediatric medicines will never be able to compete with the return from new adult medicines, and that a more radical approach and a new development model was needed. In his view, pediatric research should be publicly funded.

Menno Aarnout, the director of the international health insurer organization, AIM, also questioned the ability of current arrangements for pricing and reimbursement in Europe to ensure access to pediatric medicines. Agreement was needed on "a fair, maximum, affordable price that allows for sustainable access to pharmaceuticals." And to attain this, he envisioned more transparency of clinical data, relative effectiveness and prices, as well as closer collaboration on pricing and reimbursement methods and between regulators, health technology assessment agencies, and payers.

Absent regulatory harmonization

The regulatory framework, too, came in for some adverse comment. Industry executives wanted to see it fitting better within the global drug development process, with mechanisms that avoided the currently experienced long deferrals for starting dates for pediatric studies. They also wanted to see a system that offered greater certainty that the agreed pediatric investigation plan can be effectively completed.

Even regulators at the conference commented on continuing deficiencies in the functioning of the framework. It is not just regulators and scientists that do not always converge in their views, said Dirk Mentzer, the chair of the European Medicines Agency's (EMA) pediatric medicines committee. He also noted that national authorities were not as fast as they might be in embedding the EU's pediatric regulation firmly into their own regulators' work. He said a lot still needs to be done to overcome diverse procedures and approaches leading to divergent evaluations and decisions.

Absent decisions

Institutionally, the picture at present is that the European Commission is still conducting its gap analysis of the functioning of its orphan drug incentive scheme, which it plans to complete by March 2019, and this will feed into an overall evaluation of its support for orphans and pediatrics due for publication at the end of next year. Uncertainty, therefore, continues to reign.

— Peter O'Donnell

Q&A

THE ULTIMATE WIN-WIN: SITES INVEST, SPONSORS REWARD

Applied Clinical Trials recently spoke with Jeff Kingsley, DO, founder and CEO of IACT Health, about the importance of increased professional and technology investment at clinical trial sites. Kingsley, a frequent speaker internationally, has been faculty with the Columbus Regional Health Family Medicine Residency as well as director of several academic health system departments.

Q: You've recently presented at events on the need to raise the bar for professionalism at the site level. Could you provide a synopsis of your beliefs around this topic?

KINGSLEY: We are performing human clinical research. Certainly nothing to be taken lightly. And yet, presently, there are no rigorous standards surrounding the education and experience needed to be a clinical research coordinator or investigator. There are no minimum criteria. There is no barrier to entry.

For perspective, let's look backward a few decades in healthcare. There was a time, not so long ago, when, if you wanted to work in the emergency room, or in the intensive care unit, you could. No test. No board certification. Just a willingness and an ability to convince someone else to allow you. But today, there are board certifications and tests that are mandatory to be allowed to work in these areas of a hospital in any large facility. What changed? These are highly complex environments and they are becoming more complicated every moment as we continue to gain advancements in healthcare. There are new treatment guidelines, new therapies, and new procedures to help save lives. And the risk of human morbidity and mortality is very high.

Complexity and risk drive professionalization. Professionalization of any industry is costly. It requires a large investment into the creation of new organizations to monitor the competencies deemed important, to write the tests to assess those competencies, and to police the individuals involved in the delivery of these services. Simple jobs with low risk simply never warrant the investment to "professionalize." However, complex roles with high risk outcomes do warrant the investment.

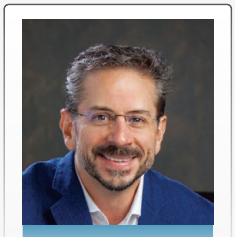
Clinical research is complex today and becoming more complex daily. We are writing longer, more convoluted protocols with adaptive designs and complicated randomization schema. Inclusion and exclusion criteria are becoming more intensive. Even unique patient-genetic profiles are now dictating study participation. And, clearly, there is risk of human morbidity and mortality. The discussions around the professionalization of our industry started as a whisper and many said, "no, it will never happen." But it turned into a conversation and is becoming a movement.

Q: Sites are notoriously known for having to deal with numerous technologies, project management changes, protocol amendments, and other changes from sponsors or CROs, which are outside of their control. How do professionals on the front lines handle these constantly shifting requirements?

KINGSLEY: Standardization improves quality. And, unfortunately, on the front lines, we have anything but standardization. What we work with on the front lines is immense variability. Sites are required to use unique technologies from each sponsor or CRO on each protocol. Many times, we have multiple different technologies being used with the same sponsor. Similarly, sponsor and CRO processes are different among protocols. This variability only increases the likelihood of errors. Airline pilots run through the exact same checklist before every flight because standardization of processes reduces errors. We do the same thing in our operating rooms before, during, and following the surgery. Our hospitals create standardized order sets because everyone agrees that standardization improves outcomes. But in research, sponsors and CROs are driving change, not the sites. If you're only doing one trial with one sponsor, you'd never see it. But if you're doing 200 trials with 50+ sponsors and 10+ CROs, the variability is immense.

Q: Can you elaborate on your views around investing in clinical research technology at your organization? Do you believe sites have an obligation to invest in the future of clinical research?

KINGSLEY: In my opinion, the coming professionalization of our industry will mandate that only professional sites can conduct research. Professional sites don't dabble in research as a hobby. They are dedicated to research as part of their career or as their full career. Those sites must invest in the infrastructure and technology needed to elevate performance in our industry. If the sites drive this investment, the sites will see standardization. Rather than a sponsor or CRO mandating use of their source document templates, delegation of authority logs, or other systems, the sites must invest in their own electronic source and regulatory document platforms and standardize that use across every protocol performed at that site. In so doing, site quality will improve.



Jeff Kingsley

However, there is a give and take involved here. Most sites won't invest in the future of research without an incentive to do so. Today, sponsors don't give sites better budgets because they're using eSource or eReg. But, I believe, they should. Site investment into these systems is an investment that produces higher quality data for the sponsor. ALCOA-CCEA (attributable, legible, contemporaneous, original, accurate, plus complete, consistent, enduring, and available) becomes easier. Integration of eSource with EDC is a reality causing seamless data transfer without the delays or transcription errors involved today. There's good data to show that certified principal investigators paired with certified coordinators produce fewer protocol deviations, enroll higher, and receive fewer FDA 483s. And yet, today, sponsors don't compensate sites better based upon certifications of the site staff.

The ultimate win for everyone is for sites to invest in infrastructure, technology, certification, and professionalization and for sponsors to reward those sites appropriately in the form of preferred study award and improved contract and budget terms.

— Staff Report

CLINICAL DATA MODEL

LEVERAGING A UNIFIED DATA MODEL TO DRIVE COLLABORATION

We all know that the clinical trials industry is beset with inefficiencies, meaning it takes too long and costs too much to bring a new medicine to the patients who need it. There are clearly many opportunities to gain efficiencies, but one area that has been a particular focus recently is the promise of technology and data.

Both pharmaceutical companies and CROs have access to a wide variety of technology and data related to the conduct of clinical trials, but in many cases a lack of sufficient standards is stifling their ability to integrate across different technologies and data sources, leaving them unable to achieve the promise of efficiencies. Instead of streamlining the decision-making process, companies spend a significant amount of time on sequential use of non-integrated technologies, on manual processes to match across data sources, and on establishing definitions of clinical trial terms to enable a like-with-like comparison and exchange of data between partners.

Recently, however, there has been a notable shift. What was once an individual company's confidential information, has now become more narrowly defined such that historical competitors are open to collaboration on data models, including common definitions and lists of values. The goal here is to leverage a single data model to enable connectivity for a broad range of clinical operations technology solutions and data, thus generating efficiencies for all players without compromising a single company's "secret sauce" (e.g., compound, protocol design, processes, data algorithms).

This article will focus on a case study example of a collaborative effort to share (upon obtaining consent) investigator, site, and study information across companies, and on the single data model that underpins it. Specifically, the article describes a single data model is being used by 15 major CROs and pharma companies to match and master data from clinical trial management systems (CTMS). Once aligned to a data model, companies are able to integrate with an end-to-end suite of clinical operations solutions. In the study planning phase, integration enables a unified view of data sources, including sharing across companies with appropriate permissions supporting trial enrollment planning, country selection, and site/investigator identification.

Unified data model

"Why has it been so hard to agree on a data model?" The answer to this is two-fold:

1) Each company installment of CTMS is unique (even when purchased from the same technology provider), so there is significant variation in data fields, names, and formats.

2) There was no way to match investigators and sites across companies and systems.

To overcome these challenges, we facilitated a series of workshops with four leading pharma companies to explore similarities and differences between companies. Through this investigation, we found there was variability in how companies structured their data from more than one direction.

- **Syntactic:** Different sets of data fields; varying nomenclature for similar data field labels; alternative vocabularies (ICD-9, MedDRA, MeSH) and terminology; non-compliance with international coding (e.g. ISO).
- **Semantic:** Different meaning for same fields (e.g., site recruitment dates), various definitions for types of data (e.g., study phase).

Because of the significant variation in each implementation, we decided to develop a unified data model, including a stand-alone file specification to which each of the companies could easily map their own internal CTMS. Ultimately, it took six months of collaboration to generate the initial specification, and the conversation is ongoing.

The specification defines:

- Data model: Their purpose, definition, format, type, size, and allowable values.
- Mappings of vocabularies and controlled lists of values (LOVs).
- The business rules that are applied when importing data files.
  - o Ensures common meaning between companies
  - o Sets the governance of allowable sharing of data between companies
  - o Enables calculations for key analytics and metrics

Data model

At a high level, the data model describes the following:

- Persons: Name, email, phone, role, training, degree
- Facilities: Name, address, phone
- Studies: Protocol number, title, phase, milestone dates, and enrollment numbers

Where possible, the field format complies with established data standards such as dates in YYYY-MM-DD format per ISO8601 and countries/regions based on ISO3166. For a large number of fields, however, a new LOV was needed to enable cross company data interoperability. Examples of where new standardized lists needed to be created include, but are not limited to:

- Degree (typically a text field in CTMS today)
- Role (unique to each company)
- Phase (company-specific variations such as Phase I, Ph 1, etc.)
- Specialty (two-level list, primary specialty and sub-specialty, applicable across all countries)
- Department type (two-level list, department and sub-department, for large research facilities)
- Study site status (unique to each company)

Unique identifier for persons, facilities

While the file specification and underlying data model and file solved the issue of producing uniform data, we also needed to build a system for matching both clinical research personnel and sites across systems to achieve an interoperable dataset. Most systems that match across sources today do so based on email; however, our experience in the clinical research space suggests that email may be missing and does not uniquely identify a person (e.g., site-level mailbox used by all or a person who works at two different sites with a separate email for each site).

** To see what process and steps were ultimately used in this unified data model example, and to read the full version of the article, visit: https://bit.ly/2RtXXUq*

— Elisa Cascade, MBA, is Chief Product Officer; Claire Sears, PhD, is Director, Product Communications, both with DrugDev

A Q&A

Under the Hood of GrantPlan 6.5: Access to Budgeting Intelligence

Shelley Douros
Associate Director
IQVIA Technologies

Learn about a unique clinical grant benchmarking solution.

Applied Clinical Trials talks with Shelley Douros, Associate Director at IQVIA Technologies, about IQVIA's GrantPlan technology, the industry-leading investigator grant fair market value benchmarking solution. She describes how GrantPlan allows users to confidently build investigator grant budgets and the enhancements available on the newly launched user-friendly GrantPlan 6.5.

Applied Clinical Trials: Could you tell us about GrantPlan?

Douros: GrantPlan is a technology solution that is used to create and negotiate clinical trial investigator grant budgets with the participating sites. The database has two main sources. The first is data from clients' executed contracts that is blinded and fed back into the system. The other main source of data is what we call PL, which is publicly available data that our engineers analyze and then apply our "secret sauce." This is my favorite part of GrantPlan because it is the only database that allows you access to this data consortium. Without the PL data, you would have data gaps, and because GrantPlan has both actual data and this additional PL data, you will never have a zero-dollar amount. This is important because you want to make sure that you have a robust budget when clients are negotiating with clinical investigator sites.

Applied Clinical Trials: What makes GrantPlan different from other fair value market investigator grant tools?

Douros: The main difference is the amount of available data with GrantPlan. All tools provide fair market value on items budgeted for within an investigator grant, which includes procedure, personnel, and site costs. Subscribers submit their final executed site budgets to the product owner. The values are then extracted, blinded, and put back into the system to serve as benchmarks.

This is where the similarities between GrantPlan and other tools end. GrantPlan subscribers conduct 76% of all global clinical trials. This means other tools are at a deficit because they don't have much robust actual data, making GrantPlan actual data superior to all others. Limiting your database by only providing actual data means users only receive Fair Market Value

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for items with submitted executed site contracts. That's a huge gap of information, especially for areas like rare diseases or uncommon procedures.

In contrast, GrantPlan provides a consortium of data that includes actual data and price list data to ensure users have holistic budgets with no gaps. Our engineers take these multiple sources of information, analyze the data, and then add our "secret sauce." Then, users can really budget for all indications and in all countries. Because we can fill in these data gaps, users don't have to search for information online or ask their clinical teams for costing guidance. So, GrantPlan provides a complete approach to budgeting.

Another huge difference is providing country-based FMV. Because other tools are solely based on actual data, they can only provide data on countries in which they received executed contracts. Meanwhile, GrantPlan suggests a country equivalent, which means it allows users access to all countries without limitations. GrantPlan includes actual data for over 60 countries and provides country equivalent costing on over 130 countries.

Applied Clinical Trials: Grant Plan 6.5 was just released. Can you tell us about your favorite feature in 6.5?

Douros: That's a hard question because there are several excellent features in 6.5. When updating GrantPlan 6.5, we focused on system usability. We want GrantPlan to give users a seamless workflow, so our engineers and development team worked on the overall design and functionality to improve the flow and optimize our users' time and effort. The user interface was also upgraded in GrantPlan 6.5.

Another huge improvement is how users can input exact durations between each visit. Previously, there was a function where you would indicate an overall estimate of time between visits. Now, users have the ability to input the precise duration between each visit and this will help those who want to start implementing standard of care.

Last, my absolute favorite addition to 6.5 is the inclusion of the initial offer and upper-limit columns, which provide flexibility when you're creating your budget guardrails. Basically, the budget builder can set budgeting and negotiation percentage parameters, which is extremely helpful. For example, if you have a $100 budget, you may want your initial budget to the site to start at $90. However, the negotiators can negotiate up to $120 without needing additional approval. In order to communicate this negotiating plan, there would be a lot of back and forth communication and several emails. Often, clients are working with multiple negotiators in numerous countries with hundreds of sites. GrantPlan 6.5 enables users to set these guardrails within the system to make for a more seamless process and consistent messaging. This is a huge benefit to our users!

Moreover, this feature will really help with transparency and will help clients start to set the stage for company-specific processes such as understanding country negotiation trends and cost savings. The upgrade itself is truly amazing, and I'm really excited about how it can help our clients focus on their internal processes and develop great strategic solutions.

Another nice feature is the ability to export data vertically. Before 6.5, you could only export data horizontally. Users have been asking for this capability so they can create an Exhibit A or Schedule A.

Applied Clinical Trials: Can you explain how the new standard-of-care feature can help users?

Douros: Adding specific durations between each visit allows for more precise standard-of-care allocations. The specific visit durations are called the duration to next visit (or DNV). Previously, users only had the option to estimate the overall time between each visit. This enhancement in 6.5 allows users to tailor visit durations to match the exact protocol requirements. This means when you're applying your standard of care, GrantPlan will accurately identify those exact visits where standard of care should be applied. This will help with compliance to ensure that you're eliminating the appearance of paying above fair market value rates.

In addition to ensuring compliance, there is also the added benefit of cost savings. I have one example where a client had a per patient procedure total of about $3,700. They then applied standard of care and reduced the cost to $3,200, which was a procedure cost savings of $496. The client had approximately 500 U.S. patients, so the total savings were close to $250,000. This feature allows clients to save money and be strategic with how they spend their money.

CLINICAL TRIAL INSIGHTS

INSIGHTS INTO OUTSOURCING PRACTICES AND OVERSIGHT EFFECTIVENESS

New study reveals that inconsistent, tactical, and reactive outsourcing practices predominate

Ken Getz

In 2017, contract research services became the single-largest category of R&D spending by pharmaceutical and biotechnology companies. Spending on outsourcing services is approaching $80 billion annually, larger even than sponsor spending on infrastructure and internal scientific and operating personnel combined.

Although a few notable top 25 pharmaceutical companies have announced plans to cut back on their CRO usage, there are many indications that CRO spending will continue to rise relatively rapidly. The overall drug development landscape continues to shed full-time positions. Since 2012, pharmaceutical and biotechnology companies have announced the elimination of nearly 40,000 positions. Nearly one-third of these position eliminations are from R&D functions. The volume of drugs in the global R&D pipeline continues to rise steadily, indicating that variable capacity obtained through outsourcing will be essential.

During the past five years, there has also been a proliferation of smaller pharmaceutical and biotechnology companies with at least one drug in active clinical testing. Of all companies sponsoring one or more clinical development programs, 61% now fall outside the ranks of the top 50 largest. Outsourcing meets a critical need for many smaller organizations that lack the personnel and experience to run clinical development programs.

Usage and oversight practice

Sponsor companies have implemented a variety of outsourcing models over the past several decades, with the goal of driving higher levels of efficiency and speed at lower fixed operating cost. Transactional models securing head count for a specific task per study are the oldest outsourcing approach. More recent models seek to achieve greater efficiency through higher levels of integration and coordination. These models leverage dedicated staffing; shared governance; integrated data; management control systems and procedures; and fewer sponsor personnel overseeing CRO execution.

To date, sponsor company use of a single or predominant outsourcing model has not been observed. Past research on outsourcing practices has shown that pharmaceutical and biotechnology companies use transactional and integrated outsourcing relationships simultaneously, mixing and matching the use of internal and contract staff across functions, varying the types of models used on a study-by-study basis.

In 2018, Tufts CSDD conducted a new study—funded by a grant from Comprehend Systems—to update benchmarks and monitor trends in outsourcing model adoption. The study also assessed oversight practices and experience—an area that to our knowledge has not been evaluated previously.

Tufts CSDD implemented the survey online among pharmaceutical and biotechnology companies between February and March. A total of 88 unique companies—a 25% response rate—completed the survey. The majority of respondents (54%) had 10 or more years of experience in their current position. Nearly 60% of respondents were in clinical operations. The remaining respondents were distributed across clinical development (17%); quality assurance/quality control and clinical compliance (14%); and vendor procurement/vendor oversight (10%). Respondents largely had global outsourcing responsibility, with two-thirds based in the U.S.

Overall, pharmaceutical and biotechnology companies report mixed levels of satisfaction with their outsourcing management capabilities and their oversight effectiveness. More than half of the survey respondents reported using three or more different outsourcing models simultaneously. This finding reflects the realities of an outsourcing environment where sponsor companies prefer to modify approaches to meet individual project needs. More than three-out-of-four (77.3%) indicate that they routinely use full-service outsourcing. Approximately half (55.7%) routinely use functional service providers and four-out-of-10 use transactional, fee-for-service models.

Oversight practices were more actively supported by middle-to-lower levels of governance—most notably operating team and project team levels. Steering and executive committee oversight was less actively used. Managing risk and ensuring regulatory compliance were the primary objectives of oversight, followed by improving individual study performance and improving CRO productivity and performance. Approximately 80% of companies indicate that they use performance metrics to evaluate oversight effectiveness. Only 12% of companies report using industry-established standard metrics.

Email was the most frequently used (82% of respondents) oversight reporting approach. Status report teleconference calls, performance dashboards, and study portals were less commonly used to support oversight and escalate issues.

Companies are the most satisfied with oversight reporting accuracy and least satisfied with the clarity and practicality of proposed resolutions. Faster issue identification and resolution and more actionable insights and recommendations were the top areas where oversight could most improve. Companies also noted the need for more executive level involvement in the oversight process.

Flexibility and execution

Despite mixed levels of satisfaction, sponsor companies are choosing to use multiple outsourcing models—from traditional to more integrated—concurrently. This approach, while offering flexibility to meet individual study needs, is highly customized. As a result, it cannot be implemented across teams and functions consistently.

Top reported oversight objectives indicate that companies are placing a premium on execution. The primary purpose of oversight is to guard against and mitigate potential risks and to ensure regulatory compliance. As such, oversight is relegated to a more reactive role and its function falls largely to the project and clinical operations teams. More strategic and proactive objectives that would enhance collaborative trust and effectiveness are considerably lower priorities at the present time.

Sponsors indicated a relative lack of senior management involvement in the oversight function. This is likely contributing to

CLINICAL TRIAL INSIGHTS

a less strategic and collaborative oversight approach, may enable more acrimonious executional interaction, and may be contributing to mixed levels of satisfaction with oversight effectiveness.

Optimization pursuits

Taken in the aggregate, over a long time horizon, sponsor performance and inefficiency—regardless of the level of outsourcing used—have not improved. Drug development speed, cost, and success rates have not gotten better. In some cases, operating conditions have worsened considerably. Ongoing Tufts CSDD research shows that the cost of drug development continues to rise steadily by nearly 9% each year. Development cycle times have gotten longer and less predictable, with a higher incidence of unplanned delays and changes. And success rates are at their lowest, with only 11% of INDs filed ultimately receiving FDA approval.

The results of this study are consistent with past research conducted by Tufts CSDD. Wide variation in outsourcing model usage within sponsor companies may be limiting the achievement of efficient and predictable performance. As a start, the application of tools and technologies would go far in helping to enable better communication, reporting, and accountability.

Meanwhile, the outsourcing landscape continues to evolve and change rapidly. Traditional outsourcing is seeing notable increases in market concentration at the same time that specialty service providers experience unprecedented growth. Consolidation among mid-sized to large contract clinical research services providers during the past five years has been brisk and it has resulted in substantial market share gains among the top 10 largest CROs. During the past seven years, Tufts CSDD estimates that the 10 largest CROs have gained approximately 12 percentage points to capture nearly 57% of the overall outsourcing market.

> Faster issue identification and resolution and more actionable insights and recommendations were the top areas where oversight could most improve.

Small niche and specialty contract service providers have enjoyed strong relative annual growth, approaching 10%. The mid-sized, full-service contract clinical services provider segment has experienced slow relative annual growth (4% between 2011 and 2017).

The largest CROs are intensifying efforts to differentiate themselves. Several are stretching their business models and including investigative site capabilities to drive scale efficiencies and economics. Some have expanded their portfolios to meet demand for higher levels of patient engagement as well as rich, advanced, and continuous data and analytics supporting learning health and research systems.

Outsourcing practices remain inconsistent and undisciplined—operating practices that invite inefficiency. These practices introduce incremental direct and indirect costs to support customized approaches. In addition, collaborative practice experience and efficiencies are isolated to individual studies and cannot scale across the development portfolio.

There is ample opportunity to drive higher levels of collaborative value through more consistent and strategic outsourcing practices. And there is no better time than now to begin. The pressure to optimize drug development performance continues to intensify as the CRO landscape continues to grow and evolve.

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

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eLEARNING:
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Using Facebook Ads to Recruit Clinical Study Participants

First column in series looks at the effectiveness of digital marketing as an outreach tool

EYE ON PATIENT ADVOCACY

The Michael J. Fox Foundation Recruitment and Retention Team

The Michael J. Fox Foundation for Parkinson's Research (MJFF) aims to speed clinical research by removing obstacles that stand in the way of therapeutic development for the Parkinson's community. In pursuit of this mission, the Foundation gathers insights from a wide range of stakeholders and uses these perspectives to enhance clinical trial processes from start to finish. In this introductory column (look for more articles in the "Eye on Patient Advocacy" series in next year's *Applied Clinical Trials* print editions), we will highlight best practices and lessons learned from the field of Parkinson's research that can be applied to clinical trials across disease states. For access to the full suite of MJFF best practices, please visit the Parkinson's Clinical Trial Companion, at bit.ly/2RWmeCq. In this month's article, we explore how digital marketing can enhance clinical trial recruitment efforts.

Background and objectives

With 80% of individuals going online to learn more about specific diseases or treatments, digital media has become a leading source of health information.[1] More and more, people use mobile devices to find this information, making it easier to gather consumer demographics, such as age, gender, and location.[2] This growing population of online users represents an opportunity for clinical researchers to engage with and recruit a broader audience at a lower cost than through traditional marketing channels.

To determine the efficacy of digital marketing as a low-cost method of recruitment, MJFF designed a pilot to recruit individuals with late-stage Parkinson's disease (PD) to Fox Insight. Fox Insight is MJFF's virtual longitudinal study aimed at better understanding the heterogeneity of the disease by collecting health information using online self-reported questionnaires and other remote data like wearable sensors and personalized genetic testing results. Fox Insight is open to people with and without PD. Objectives for the marketing pilot were to: 1) increase the volume of enrolled participants; 2) target and enroll participants at specific stages of disease; and 3) examine costs of recruitment using digital methods.

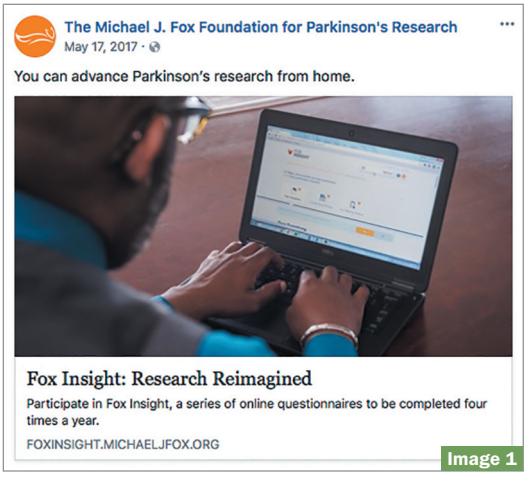

Image 1

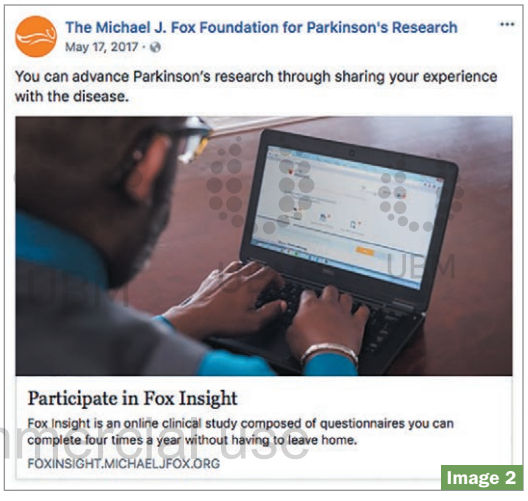

Image 2

Methods

Participants

To ensure that Fox Insight accurately reflects the Parkinson's community, it is imperative that individuals at different stages of disease are equally represented in the study. At traditional brick and mortar research sites, individuals with later-stage PD are often underrepresented due to factors[3] such as advanced age[4] and motor and non-motor symptoms. To address this sampling challenge, the Fox Insight study team identified individuals with late-stage PD as an important target population for the marketing pilot. To be shown an ad, prospective participants had to meet the following eligibility criteria:

- Currently living in the U.S.
- Age 60 or older

- Indicated "Parkinson's disease awareness" as an individual interest and selected interests in subject areas related to PD or clinical trials (e.g., clinical trials, PD symptoms, and PD organizations) on Facebook
- Not already involved in the MJFF online community (e.g., had not visited the MJFF website in the past 30 days and had not ever "liked" the MJFF Facebook page)

Facebook was selected because of its vast reach, many targeting capabilities,[5] and tracking techniques that enabled referral source attribution for those individuals recruited to Fox Insight.

Materials

Two types of Facebook ads were designed for the marketing pilot. One was aimed at individuals ("me" language) and the other emphasized the collective effort of clinical research ("we" language). Two subthemes were tested for each type of ad.

- *Individual (me):* Language appealed to users on an individual level, to be empowered to impact research by participating in an online clinical study (Fox Insight). An image of an individual participating in Fox Insight on their computer accompanied these ad variations.
  - Subtheme: Research Reimagined (see image 1 on facing page)
  - Subtheme: Lead the Way (see Image 2 on facing page)
- *Collective (we):* Language encouraged the user to contribute to a larger cause by participating in an online clinical study (Fox Insight). An image of a family sitting together in a waiting room accompanied these ad variations.
  - Subtheme: Join a Collective Goal (see Image 3)
  - Subtheme: Impact the Future (see Image 4)

Design and procedures

The different ad variations were tested in three sequential phases over a period of six weeks. Each phase cost approximately $8,000. At the end of each phase, the number of individuals recruited to Fox Insight along with the cost per recruit was evaluated.

Phase 1

- *Timing:* Weeks one and two; ads shown approximately twice a day.
- *Variables tested:* Compared the efficacy of the four different ad variations to determine if users were more responsive to language/image combinations that fell in the individual or the collective categories, and within these categories, which messaging was most effective.

Phase 2

- *Timing:* Weeks three and four; ads shown approximately twice a day.
- *Variables tested:* Compared levels of responsiveness to the winning ad variation from phase 1 among individuals with different Facebook interests. The two interest groups compared were: 1) individuals with interests in PD awareness and terms related to PD symptoms; and 2) individuals with interests in Parkinson's disease awareness and terms related to clinical research. The two interest groups were mutually exclusive. Interest-targeting is made possible on Facebook by information that individuals add to their timeline, keywords associated with pages they like, apps they use, or ads they have clicked on.

Image 3

Image 4

Phase 3

- *Timing:* Weeks five and six; ads shown approximately twice a day. *Variables tested:* Assessed the efficacy of the winning ad variation from phase 1 among a broad target audience without any interests defined.

Fox Insight enrollment after each phase of marketing pilots was compared to baseline (a six-week period, pre-intervention) where no special promotion of Fox Insight took place, and recruitment was only facilitated through MJFF educational content and Fox Trial Finder, a smart-match tool. Campaign success was primarily assessed using participants' self-reported date of diagnosis. Additional validation on stage of disease was conducted using information from the Fox Insight platform about medication history and symptoms

based on the Non-motor Symptoms Questionnaire (NMS-quest) and the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part II).

Results

Total enrollment

Compared to baseline (n=123), the marketing pilot significantly increased (825%) participant enrollment (n=1,138). Of those newly enrolled, 46% were individuals with PD, and 760 (67%) came directly from the Facebook ads (i.e., clicked on an ad link and registered for the study). Those registrants who did not come directly from Facebook (33%) may have been exposed to the Facebook ads during the six-week pilot but entered through other channels such as MJFF educational content or Fox Trial Finder.

Population-specific targeting

The Fox Insight Facebook Ads Campaign was successful in targeting and recruiting individuals with late-stage Parkinson's disease as evidenced by an increase in the number of individuals who met the following criteria compared to baseline (see Figure 1):

- PD diagnosis of 10 or more years
- A score of 25 or higher on the MDS-UPDRS (Part II)
- A Non-motor Symptoms Questionnaire (NMS quest) score of 13 or higher

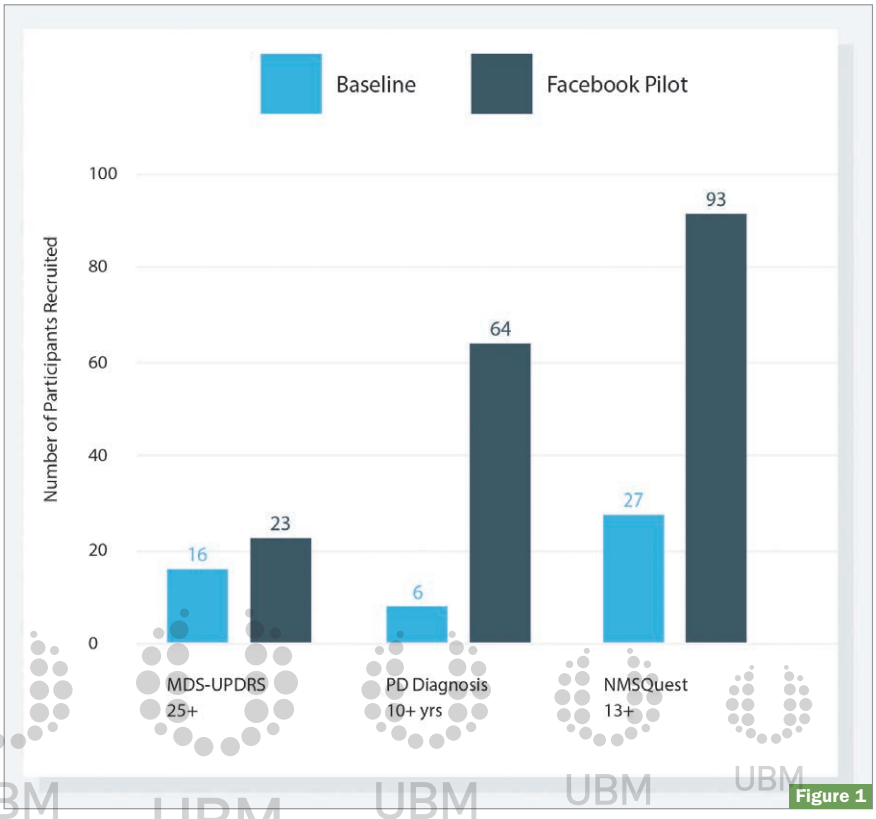

Figure 1

Recruitment costs

The cost per conversion (i.e., the total cost of advertising/# of enrollees) of those individuals who came directly from Facebook (n=760) was $31.51/per enrollee, an incremental increase compared to traditional direct-mail methods ($30.45/per enrollee) within a similar population.[6]

Discussion and conclusion

Digital marketing is an effective outreach tool with substantial capacity to increase access to and engagement with prospective research participants. The success of the digital marketing pilot to recruit individuals with late-stage Parkinson's disease indicates potential applications for recruiting individuals from diverse racial and socioeconomic backgrounds who are also underrepresented in clinical research, and for driving broad populations of prospective participants from digital advertisements to online study resources. Finally, the comparability in cost per conversion of digital marketing to that of traditional methods demonstrates its utility as a tactic that clinical trial teams can employ as part of a comprehensive recruitment strategy.

The MJFF Recruitment and Retention Team includes: *Christine Cowles, MPH, Senior Associate Director; Sarah Berk, MPH, Associate Director; and Bernadette Siddiqi, MA, Associate Director; all with The Michael J. Fox Foundation in New York, NY. To contact the MJFF Recruitment and Retention Team, email: trialsupport@michaeljfox.org*

References

1. Fox, Susannah. "The Social Life of Health Information, 2011 | Pew Research Center." *Pew Research Center: Internet, Science & Tech*, Jan. 23, 2014, www.pewinternet.org/2011/05/12/the-social-life-of-health-information-2011/.
2. Stempel, Dan. "2016 Trends for Digital Recruitment in Clinical Trials." *Medical Marketing Insights*, 2016, www.mdconnectinc.com/medical-marketing-insights/2016-trends-for-digital-recruitment-in-clinical-trials.
3. Mody, Lona, et al. "Recruitment and Retention of Older Adults in Aging Research." *Journal of the American Geriatrics Society*, vol. 56, no. 12, 2008, pp. 2340–2348., doi:10.1111/j.1532-5415.2008.02015.x.
4. Varanese, Sara, et al. "Treatment of Advanced Parkinson's Disease." *Parkinson's Disease*, vol. 2010, 2010, pp. 1–9., doi:10.4061/2010/480260.
5. Stempel, Dan. "How Digital Marketing Lowers Clinical Trial Recruitment Costs." *Medical Marketing Insights*, 2017, www.mdconnectinc.com/medical-marketing-insights/digital-marketing-lowers-clinical-trial-recruitment-costs.
6. Stephenson, Hugo, Bharmal, Murtuza. "Direct-to-Patient Enrollment Strategies." *Applied Clinical Trials*, Feb. 12, 2015, www.appliedclinicaltrialsonline.com/direct-patient-enrollment-strategies?id=&sk=&date=&pageID=4.

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Implementing eClinical Tools: A Daunting Task

Survey highlights thoughts on digital integration, managing data sources

Lisa Henderson

SURVEY SPOTLIGHT

This fall, our survey partner SCORR Marketing and *Applied Clinical Trials* set out to find out what the eClinical technology landscape looked like. The full results of the survey is downloadable here: https://bit.ly/2rkp0WE. Like other recent surveys and conferences conducted in eClinical (read here: https://bit.ly/2ZG2FaJ), an inconsistent and frustrating picture emerged.

And it is no wonder. Bracken Marketing, an agency that is dedicated to eClinical providers, offered this infographic of over 190 vendors in the eClinical space, segmented by their core expertise: https://bit.ly/2KORyAF. That's a lot of choices and clinical trial parts to be managing. For example, our survey found that 54% respondents said their relevant clinical function team was the primary decision-maker on a software purchase, as well as the person who determined if a solution was needed at all. Anecdotally, this has led to a phenomenon of duplicate software purchases at large pharma or situations of duplicate efforts by therapeutic teams in reviewing technology products. In fact, in the article linked above, Shelley Padgett, senior director of IT at Eli Lilly & Co., observed the exploding number of third-party solutions involved in the company's infrastructure, as well as the amount of data and platforms. Her goal now? To establish a model that brings together its workflows but with a smaller set of platforms.

Quality concerns

Similarly, in an article by Jim Streeter, global vice president, life sciences product strategy, Oracle Health Sciences, which is in this issue (see page 20) and based on a survey by the company, it revealed that more than half of the clinical data professionals surveyed are not confident in the quality and completeness of their clinical data from an audit and compliance perspective. And, again, not a surprising revelation, given the number of vendors in the eClinical space. The Oracle survey reported that 50% of respondent companies have between one to five data sources for a typical clinical trial; 37% between six to 10; 7% have 11 to 15, and 6% have more than 15 data sources.

This fact was also not lost on the respondents to our survey. To the question, "Does your organization currently have an initiative to integrate its clinical trial systems and processes?" 55% responded yes; 25% responded they were in the planning stages; and 20% said they did not or were unsure.

On a different note, however, our survey found 47% and 27% of respondents found the benefits of digital data collection to their organization to be improved data

HURDLES TO MULTISYSTEM DATA COLLECTION

Integration across applications	33.3%
Managing data across applications	24.2%
Time required to learn different systems	21.2%
Other	12.1%
Inconsistency of data reporting	6.2%
Meeting compliance standards	3%

Source: *Applied Clinical Trials and SCORR Marketing survey, October 2018.*

The response breakdown to survey question: "What has been your organization's biggest challenge in collecting digital data across multiple applications?" Note: "Other" includes ability to get data—systems are mainly CROs/vendors; no electronic system, and many of the above.

quality and access to real-time data, respectively. Further, 40% of the respondents noted that, overall, these technological advances provide better quality data, and 25% optimistically say that technology leads to more cost-effective clinical trials.

RBM impact limited

One area of clinical trials that seem poised to take off and provide that promised cost-effectiveness was risk-based monitoring (RBM). Five years ago, the FDA initiated back-to-back guidances on RBM and then using eSource in clinical research. Unfortunately, as this issue's article, Barriers to RBM (see page 22), as well as this peer-reviewed article online: https://bit.ly/2BN3TlYg note, that success has not been found. From the latter article, the authors state: "Since publication of the regulatory guidance on risk-based monitoring five years ago, the concept of centralized monitoring has developed amid the emergence of technological enablers that make clinical research more data-driven than ever. ...Despite its unique potential for improving the quality of clinical trials, centralized monitoring can appear so technical that sponsors often elect to renounce its use in favor of costly and less efficient traditional monitoring methods."

And in the former article, the barriers to RBM adoption ranged the gamut, but technological barriers included having the technology tools work together is difficult; difficult to understand the different RBM approaches; difficult to choose which approach is best for our organization; and technology tools are confusing, difficult to know which are needed.

To the last point—technology tools are confusing and it's difficult to know which are needed—that is indeed daunting. And not just relegated to choices in monitoring. In our survey, obstacles that have hindered your organization from implementing technological and eClinical solutions included, in order of highest to lowest, cost; fear of change; data integrity/security; insufficient collaboration; lack of resources; and lack of internal support/training.

> This has led to a phenomenon of duplicate software purchases at large pharma or situations of duplicate efforts by therapeutic teams in reviewing technology products.

Level-out looms?

With the future of clinical trials looking to move studies closer to the patient's point of care, become increasingly smaller and more targeted, and introduce analytics and more reliable measures of mHealth to help virtualize trials, the plethora of software solutions may even out and become less daunting. In the meantime, companies can be assured they are, in many cases, gaining the benefits they originally hoped for in their digital choice, and comforted that others face the same confusion.

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3. Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS	1,916	2,884
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H. Total (Sum of 15f and g)	11,505	11,260
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Data Dilemmas in Clinical Trials Continue

Jim Streeter

Survey uncovers key findings amid today's explosion of data volume and sources—and the added complexity in managing clinical data.

DATA MANAGEMENT

Every time you order an Uber, a chain of transactions take place, from matching you to your driver and mapping your location to generating notifications and processing payment. A treasure trove of data is generated. On the nights you decide to stay in, you might stream a movie on Apple TV or Netflix. Digital rights are managed, payments are made, and a record is logged so when you sift through your iTunes receipts or Netflix bill, you can recall what you watched and how much you spent. It seems data is created by every move we make and it's reorganizing entire industries like transportation and entertainment.

For those of us in the world of life sciences, the inherent value of data is not new. This industry doesn't exist without data. Having clean, high-quality, clinical trial results data to send to regulators enables biopharmas, contract research organizations (CROs), and medical device companies to prove the safety and efficacy of new therapies and make historic contributions to advance medicine. In addition to capturing data related to the safety and efficacy of drugs in clinical trials, data on patients is collected as part of the clinical trial process. From vitals and lab data to patient diary data, this data must be clean, high-quality, and consistent or it can stall the progress of a clinical trial.

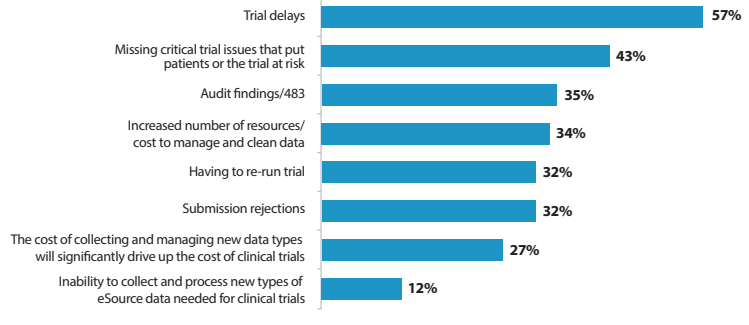
We're in the midst of a data explosion and we have more data than we know what to do with. Clinical data is coming in new formats and there's a shortage of data scientists who can interpret and analyze it for meaningful use. A study from Tufts University shows that the number of data points included in a Phase III study today has doubled from 10-years prior. As the volume of trial data continues to grow, and the variety of data and sources continue to increase, clinical data management challenges are becoming more complex.

Earlier this year, a global survey was conducted to determine the crucial "hype versus reality" factor for clinical operations as it relates to data management. Surveyed were clinical researchers, data scientists, and clinical programmers from biopharma organizations, CROs, and a small percentage of medical device companies.

Data-Issue Fallout

Research Results: Data Governance Issues

What are the most critical problems that can result from clinical data issues?



Source: Oracle

Figure 1. Trial delays and issues slipping through top the list.

Respondents were from around the globe—61% from North America, 20% from Asia-Pacific, and 17% from Europe. The results, outlined here, tell us where issues exist and what to prioritize over the next five years.

In a nutshell, the survey revealed that more than half of the clinical data professionals surveyed are not confident in the quality and completeness of their clinical data from an audit and compliance perspective. Costly data preparation, slow data reconciliation, and poor data quality are hindering drug development efforts for life-saving therapies.

Fifty-seven percent of respondents believe that their clinical data issues cause trial delays (see Figure 1 on facing page).

Additionally, 81% of respondents cited data governance issues as the biggest challenge in meeting regulatory compliance, and more than half are not confident in the quality or completeness of their clinical data when preparing for regulatory review. Figure 2 shows the results of respondents when asked about the biggest risks to a trial as a result of data governance issues.

The respondents also named inconsistent data, missing data, and patients missing visits as the top three most critical problems to catch when looking at clinical trial data.

About a third of respondents don't feel like they have tight controls over their clinical trial data—they can't see the entire picture of what is available, it is hard to get errors corrected, and challenges remain with searching for information.

When asked how long it takes to receive clinical trial data from internal and external partners, once it has been requested, the survey revealed that electronic data capture (EDC) and laboratory data have the fastest access times, while emerging and less standardized data sources such as mHealth/internet of things (IoT) and biomarker data had the longest delivery times (see Figure 3). Evidence is showing that it is taking too long to get these new forms of data.

Lack of timely access to clinical data has other repercussions related to not being able to detect problems. As it relates to what issues might go undetected due to lack of timely access to data, 68% of respondents said protocol issues, 54% cited enrollment issues, and 43% said it could result in skewed trial results.

Managing clinical trial data is manual because the sources are diverse and siloed – some study teams have to pull data from more than 15 data sources. A total of 95% of respondents acknowledged that manual effort was involved in aggregating, cleaning, and transforming the data.

Finally, when asked about the future outlook for clinical data collection and management, 37% of respondents indicated that the most urgent challenge around clinical trial data will be the management of mHealth data. In addition, finding resources that understand how to manage and clean data was seen as the second-most important issue to address in the near future.

The data explosion puts more power in our hands than ever and has the power to bring more drugs to market faster, yet it introduces enormous challenges in terms of data governance and process. Clinical researchers shouldn't have to spend time and resources fixing data issues that technology was built to handle. Technology can, and should, be used to eliminate unnecessary manual intervention, improve data governance, and mitigate risk so we can get therapies in the hands of patients who are waiting without delay.

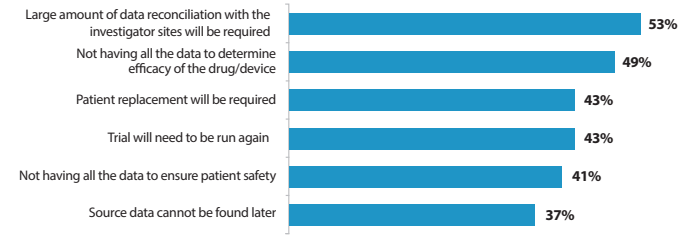
Imagine a clinical R&D world where clean, organized clinical data is available in real-time, to everyone who needs it. Insight can be uncovered, decisions can be made and time and money can be saved. But more importantly, delays in clinical trials can be reduced, cutting the time it takes to get new drugs to the market. This is the goal, and this is why we need to continue to innovate and improve technology in clinical trials.

Jim Streeter *is Global Vice President, Life Sciences Product Strategy, Oracle Health Sciences*

Data Governance and Risk

Research Results: Data Governance Issues

What are the biggest risks to a clinical trial caused by inconsistent or incomplete clinical trial data?



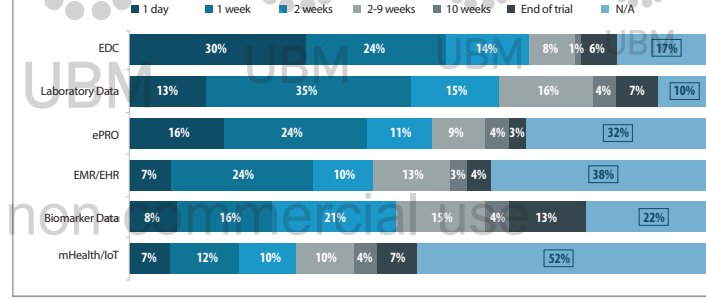
Source: Oracle

Figure 2. Having to reconcile large amounts of data with sites was reported as the No. 1 risk.

Delivery Differences

Research Results: Lack of Timely Access to Clinical Data

How long does it take to receive clinical trial data from internal and external partners, once it has been requested?



Source: Oracle

Figure 3. Data delivery times among range of data sources.

Risk-Based Monitoring: Barriers to Adoption

Penelope K. Manasco, MD

Examining the barriers, challenges, and outcomes to determine the effectiveness of different RBM implementation approaches.

In April and May 2018, I developed and conducted a survey of pharma, biotech, and CRO staff to better understand the barriers to adopting risk-based monitoring (RBM). I performed these tasks as part of my role as an expert on an advisory panel to the FDA concerning RBM issues.

Fifty-one people responded to the survey. Participant organizations include CROs (21); sponsors (23); and other vendors (7). One respondent answered the survey twice. Only one of the responses was counted. One sponsor had two respondents. That sponsor was counted once for items such as whether RBM was adopted, but all responses for barriers to adoption were collected. The survey included representatives from large, mid-sized, and small pharma/biotechs, and vaccines and medical device companies. The CRO category included large, mid-sized, and small/niche CROs and contract monitors. The "other vendor" classification included consultants (i.e., clinical trial managers, data managers), an independent review board (IRB) representative, a representative from a site organization, and technology vendors.

CROs adopted RBM at a slightly higher rate (71%) than sponsors (64%). Of those that did not adopt RBM, most were small/niche CROs and small biotech companies, though one mid-sized pharma had not adopted RBM.

All but one of the CROs that had not adopted RBM and all of the sponsors that had not adopted RBM were small companies.

Different RBM definitions

Nearly every respondent defined RBM differently and proposed a different RBM implementation approach. The lack of a common RBM definition and understanding of what RBM does represented critical barriers to adopting the method.

Many of the definitions and implementation approaches included reduced source data verification (SDV), SDV only of critical endpoints, and terms such as central monitoring of case report forms (CRFs), but most still depended on on-site monitoring. Other RBM definitions included using key risk indicators (KRIs) and other statistical methods to determine the need for and frequency of on-site visits.

Some companies incorporated approaches that did not focus on SDV. They, instead, centered on identifying risks, developing study-specific reporting to conduct remote review, and developing risk mitigation approaches.

RBM implementation approaches could include more than one method. More companies adopted a hybrid approach rather than using strict RBM principles; however, the use of the different monitoring approaches was similar. Forty one of the responses included SDV or remote eCRF review. Other methods used included KRIs, statistical outliers, and protocol-specific reports of high-risk data. Of interest, more companies noted using KRIs rather than protocol-specific reports of high-risk data.

Barriers to RBM adoption

The two most common barriers to RBM adoption reported most frequently included the concern that it was too risky to eliminate SDV and the confusing definitions of RBM. Several barriers focused on the implementation challenges:

- Too complicated
- Don't have the tools
- Approaches, processes, and training implications of changing processes

Finally, the concern about audits after the trial was also reported by multiple respondents.

Another barrier mentioned throughout the survey involved the role of senior management. More specifically, these comments addressed the need to have senior

management understand the RBM process, the RBM focus on quality, and the support needed to conduct a major change initiative.

Challenges to implementing RBM

In many cases, adopting RBM is a large organizational challenge. For those companies that have adopted RBM, the most common challenges to implementing RBM include (with number of respondents):

- Having the technology tools work together is difficult (9)
- Trainings must be designed for all team members (8)
- Monitor resistance to RBM (7)
- Difficult to understand the different RBM approaches (7)
- Skills for monitors are different (6)
- Skills for project managers are different (6)
- SOPs are not written for new approach (6)
- Senior management does not understand the process differences (6)
- Difficult to choose which approach is best for our organization (6)
- Technology tools are confusing, difficult to know which are needed (6)
- Operational metrics are different (5)

Outcomes

Table 1 illustrates the outcomes reported from implementing RBM. This table also includes a determination of whether the outcome was positive or negative. "Higher costs" was an option listed, but no respondent reported it as a positive or negative outcome.

There were more positive outcomes than negative outcomes. The highest reported positive outcomes were for "cleaner data" and "issues identified and corrected faster." "Key risk indicators helped to focus monitors on specific areas" was also reported frequently, although one respondent reported that KRIs were a disappointment.

The most common negative outcomes were related to monitoring issues. Site adoption was split between negative and positive outcomes. This likely reflects the different approaches to implement RBM. In our experience, the site responses to implementing RBM have been overwhelmingly positive.

Risk-Based Monitoring Outcomes

	RBM	POSITIVE	NEGATIVE
Better outcomes	1	1	
Fewer deviations	4	4	
Cleaner data	8	8	
Identified and corrected issues faster	9	9	
Lower costs	3	3	
Fewer audit findings	2	2	
Higher costs	0		
Better insights into trial conduct	3	3	
Shorter time for database lock	4		
Managing the study was harder because our standard management approaches don't align with RBM	5		5
Key risk indicators			
Key risk indicators were a disappointment	1		1
Key risk indicators helped focus monitors on specific areas	7	7	
Monitoring issues			
Monitors did not know how to evaluate findings from central review	4		4
Monitors had difficulty focusing only on high-risk data	11		11
Monitors insisted on SDVing all or most of the data	5		5
Monitors insisted on complete source review	3		3
Site response			
Sites were unhappy because they did not perceive they had enough support	2		2
Sites appreciated getting faster feedback	1	1	
Sites definitely do not like having to do their own QC!	1		1
TOTAL		38	32

Source: Manasco

Table 1. Outcomes reported from implementing RBM.

What could regulators do to help implement RBM?

We asked the respondents what regulators could do to support RBM implementation. Their results focused on the following areas:

- More examples of how to implement RBM successfully, including lessons learned, best practices, training, Q&As, and white papers.
- Audit advice—what will be audited; uniform interpretation and advice.

Some respondents wanted a set of approved RBM tools and processes that could be adopted across CROs. While recommended by respondents, this does not align with regulators' remit or standard practices.

What could industry do to help implement RBM?

From an industry adoption perspective, several respondents highlighted the importance of change management and executive involvement in adopting RBM. While not mentioned in the survey, several executives at small companies privately commented that investors had requested their organization keep their oversight methods "as they have always done it" and not adopt RBM; arguably to reduce costs. Other executives privately noted that some CROs have discouraged them from adopting RBM, because it means less monitoring income for the CRO.

Publishing examples of best practices in implementing RBM and developing a dialog with regulators to discuss real-world examples were two examples of how the industry could enhance and advance adopting RBM and the processes—moving it from theory to adoption. In addition, respondent thought groups, such as CITI and TransCelerate BioPharma, could facilitate this dialog with regulators. TransCelerate has generously provided its thoughts on adopting RBM, but much of its input focuses on large organizations and may be less applicable to small companies.

Additionally, sharing examples of systems and approaches that have worked was considered an important tool to support RBM adoption.

Discussion

The variability in RBM definitions and RBM implementation approaches was surprising and listed as one of the two most common barriers to adopting RBM. Since each RBM approach will have varying ability to detect "errors that matter," this complicates the discussion of implementation and outcomes from RBM.

For instance, if one company merely decreases the amount of SDV to "critical data fields," they will have a much lower ability to detect trends that can affect study outcomes and subject safety when

compared to an implementation approach that includes trend analysis and specific analytic tools to detect "errors that matter."

There was overwhelming interest in publications that provided lessons learned and best practices of RBM implementation. Defining specific RBM methods and testing their effectiveness is critical to determine which method identifies which errors, and which method provides the best outcomes. This clear, unmet medical need affects more than 100,000 study participants in pivotal clinical trials per year; approximately 30% were from the U.S. in 2015.[1]

The second-most common barrier to adoption was: "Too risky to eliminate, SDV are standard processes that worked well." For years, the pharma/biotech/device/and vaccines industries have used SDV, a method in place for nearly 30 years without being tested for effectiveness. The RBM and ICHE6(R2) changes in GCP guidance by regulators[2,3,4,5] indicate they think the current methods have not worked well. In addition, the more than 33 complete response letters from January 2017 to May 2018 also support the fact that previous successes from unproven monitoring methods do not indicate continued success.[6]

Applied Clinical Trials recently published the first head-to-head comparison between traditional SDV and one method of RBM (i.e, the MANA Method), showing superiority of the RBM approach.[7] We hope this first article to address the subject will be one of many publications that uses data to evaluate the effectiveness of different oversight methods.

Two interesting implementation findings that affect effectiveness of RBM implementation were identified by the survey and through personal communications.

- There is a disconnect between RBM adoption and adoption of technologies that facilitate the rapid, remote oversight envisioned in the RBM and eSource guidance. The findings of the technology adoption will be presented in a future, separate publication, but many companies have not adopted the tools that allow for remote review of data and documents.
- RBM has been implemented only in monitoring groups within many organizations, without including the rest of the review team. Monitors conduct oversight using "RBM" methods while data managers use traditional data cleaning methods. This can precipitate significant organizational and data flow challenges, not to mention potentially higher costs if data managers query every data point, rather than focus on the errors that matter.

There is a clear need for open and regular dialog concerning these findings, between regulators (including the auditing portion of the organization), sponsor companies, and CROs. If we look at other complex implementation of new science and technology for guidance, the Pharmacogenetics Working Group, developed in the late 1990s with regulators across the world and pharma and biotech companies, could be an effective model. A second example would be the dialog between regulators and sponsors around the early development of HIV therapies. In both instances, the organizations worked on policies, interpretation of new methods, and how best to submit and interpret data.

Another resource that would advance the development of optimally effective risk-based oversight methods would involve the creation of anonymized reference study datasets provided by the FDA or NIH. This would allow everyone to evaluate the effectiveness of their different oversight methods to detect errors that matter versus the reference study data sets. By having common reference "studies," the industry could develop and compare different oversight approaches' ability to detect errors that matter, making all studies safer for study participants.

Finally, supporting the research and publication of data-driven comparisons of different oversight methods will help the industry adopt proven oversight methods.

Summary

This 2018 survey findings showed that approximately two thirds of sponsor respondents and three quarters of CROs have adopted some type of RBM. Small pharma/biotech and small CROs were the main organizations that have not adopted RBM in the five years since the 2013 FDA and European Medicines Agency (EMA) releases of recommendations for adopting a risk-based approach to monitoring. [2,3]

A wide variety of implementation approaches have been adopted, with varying ability to detect "errors that matter." A significant, unmet medical need exists to test and publish data to determine the effectiveness of the different RBM implementation approaches. This would help the industry make informed decisions about how to best protect study participants' safety and obtain scientifically valid data to support the delivery of new medicines for patients.

References

1. Global Participation in Clinical Trial Report 2015-2016. FDA/DHHS, July 2017. https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM570195.pdf
2. Guidance for Industry: Oversight of Clinical Investigations—Risk-Based Approach to Monitoring. FDA/HHS August 2013. https://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf
3. Reflection paper on risk-based quality management in clinical trials. European Medicines Agency, November 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf
4. ICHE6(R2) Revision 2-adopted guidance EMA/CHMP/ICH/135/1995. June 14, 2017. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001251.jsp&mid=
5. E6(R2) Good Clinical Practice: Integrated Addendum to ICHE6(R2): Guidance for Industry. FDA/HHS March 2018. https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf
6. Complete Response Letters (CRLs): Big Trouble for Small Pharma. June 2018. https://camargopharma.com/2018/06/complete-response-letters-crls/
7. Manasco et al. A Comparison of Risk-Based Monitoring and Remote Trial Management versus SDV in a Phase IV Pediatric Vaccine Trial. *Applied Clinical Trials* online, Sept. 28, 2018. http://www.appliedclinicaltrialsonline.com/comparing-risk-based-monitoring-and-remote-trial-management-vs-sdv?pageID=1

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PV Software is Having Its 'Salesforce' Moment

Jim Davis

With cloud-based software dominating data systems, on-premise installations still exist and command the pharmacovigilance software market.

Salesforce officially launched in February 2000 at DEMO 2000, the then-premier launch venue for new technologies. The "End of Software" marketing promotion that accompanied the launch was nothing short of extraordinary, replete with a party where guests were required to bring a piece of physical software to throw in a gigantic trash bin and mock protests by hired actors at competitor client events declaring software obsolete.

Salesforce, for those readers that may not know, is considered the first cloud-based, software-as-a-service (SaaS) product to disrupt a large market- customer relationship management (CRM). Salesforce.com is now the bellwether in the CRM space, leading and continuing to define new markets for the Salesforce platform.

Prior to its launch in 2000, legacy vendors such as Seibel Systems (acquired by Oracle in 2006) dominated CRM with on-premise servers and software, long and complicated implementations, and equally slow and complicated user experiences. Salesforce came along with cloud-based storage, almost instantaneous implementation, a web-based user interface that could be rapidly iterated as web technology advanced, and killer marketing. The rest, as they say, is history. At the time of writing, Salesforce (NYSE: CRM) had a market cap of around $100 billion.

So, what does the CRM market have to do with pharmacovigilance (PV)? A lot actually. The parallels are striking, with some of the same market players, the same story lines, and as argued ahead, the same results.

A brief history of PV software

Electronic databases have long existed for the storage and capture of individual case safety reports (ICSRs)

> *"The Internet is really neat … Software is obsolete! Red rover, red rover, software is over!"*
>
> *- Mock protesters at a Siebel Systems user conference in 2000*

that are generated both within clinical trials and from spontaneous reporting. In the late 1990s, this space was dominated by organizations such as Relsys, Phase Forward, Aris Global, and, to a lesser extent, Oracle. The companies provided software that paired with the database to capture ICSRs and to transmit the ICSRs to regulatory authorities such as FDA. Analysis of these data were more difficult.

Statistical methods for safety signaling were in their infancy and computer systems that could process the data efficiently were not resource efficient, both in cost and time.

Datamining started to become more mainstream in 1999 with a study that was funded by FDA and published in *The American Statistician*, entitled "Bayesian Data Mining in Large Frequency Tables, with an Application to the FDA Spontaneous Reporting System."[1] Technology was developed by organizations like Lincoln Technologies to take advantage of advances in computing power to apply new statistical methods at scale. In the mid-late 2000s, consolidation in the space started to occur. In 2005, Phase Forward acquired Lincoln Technologies to advance the company's data and analytics platform. In 2008, Oracle, in line with its sector-specific growth strategy, honed its sights on drug safety and bought Relsys, and then later in 2010, acquired Phase Forward.

The enterprise goliath

With its acquisitions, Oracle became the PV software market goliath, eventually consolidating all of the brands into its Oracle Health Sciences suite of applications, and specifically bringing the database and capture software under the ARGUS brand and the data, analytics, and workflow software under the organization's Empirica brand.

In 2018, by all accounts, Oracle remains the market share leader. ARGUS and Empirica software have been synonymous with "drug safety database" and "PV software" for the past 10 years. Oracle has, unsurprisingly, taken several steps to engrain both ARGUS and Empirica into the PV ecosystem.

Being Oracle, the company certainly knows what enterprise IT wants and needs. On-premise servers (and more so now, Oracle's cloud servers) and the software that runs off of these servers are highly customizable, configurable, and designed with the Fortune 500 in mind. This level of complexity means that there needs to be a small army of in-house database and software engineers that are dedicated to keeping ARGUS and Empirica up and running with maintenance, patching, updates, compliance, etc.

Even if you are one of the only 12 pharma companies in the Fortune 500, you most likely need to outsource some of these back-office tasks. Oracle knows this and welcomes it. By creating Oracle Gold Partners and other designations that license a third-party to resell Oracle products, Oracle has created a remarkably robust closed-loop sales channel. With hundreds of partners that depend on Oracle for their own business revenue, there is ample motivation to keep ARGUS and Empirica right where they are.

Sound familiar? This is exactly the challenge that Salesforce faced when coming to market, right down to the same exact Oracle (then Seibel) strategies. The pitch to those that were willing to listen back in 2000 was that spending 90% of your technology budget on maintaining systems of record was a bad idea and that firms need to focus on front-end services-based differentiators that are revenue builders, and not just back-end infrastructure. Salesforce hammered this point home by making its platform simple to implement without the help of IT and with a front-end UX/UI that their end-users would actually want to use.

Can the same approach that Salesforce took in 2000 work for PV software in 2018?

The paradigm shift in PV software

In the past 18 years since Salesforce began its battle to take down the CRM goliath, the market for software-as-a-service (SaaS) has changed dramatically, as have the products that companies have brought to market.

The SaaS model has become so commonplace that even Salesforce itself had to clarify back in 2015 that "No Software" really meant, *"No legacy software, just cloud software."* SaaS and software are now synonymous, in all but a few cases. PV software is one of those few cases. While the software itself is no longer shipped via a CD-ROM, and it's been well documented that Oracle is making its shift to the cloud, existing on-premise installations still dominate the market and even new cloud-based options are still just remote servers, with similar software installation.

Why has PV software lagged behind? First and foremost, the world of PV is one of extensive regulations that up until recently have seemed to be always changing. A significant repository of standard operating procedures and required process documentation paperwork is necessary to pass any regulatory inquiry or audit. Both IT and business have had to focus on making sure what was in place was compliant.

Second, PV has historically been seen as a cost center within an organization, existing solely to fulfill the obligations that were required of them. Thus, a legacy system of record was all that was seen as necessary. Enough to capture ICSRs, do the minimally required aggregate signal detection to be included in periodic reports, and record actions taken in the process of managing that signal.

There are other companies that have worked to gain market share from Oracle. For data capture, companies such as ArisGlobal, largely seen as Oracle's most significant competition, has begun to make technological advances to create efficiencies. Smaller companies as well, like AgilePV, AB-Cube, and My Meds and Me, are working to create differentiated platforms to focus on case intake and processing. Vendors such as RxLogix, CommonWealth Informatics (recently acquired by Genpact), and this author's company, Advera Health Analytics, have built analytics and workflow platforms that have begun to make an impact on the market. However, as a result of both the obstacles that Oracle tatically put in place, as well as the market barriers discussed earlier, the impact has been minimal.

> In order to generate insight, appropriate tools need to be in place that are accessible to more than just a select few power users, in a select few resource capable companies.

Very recently, however, a shift has begun to occur. The last of the good pharmacovigilance practices (GVP) requirements have gone into effect. Big data has gone mainstream. And forced by demands by their customers, pharmaceutical companies are being asked to generate insight as it pertains to safety.

The last point is, in my view, the most important. In order to generate insight, appropriate tools need to be in place that are accessible to more than just a select few power users, in a select few resource capable companies.

Remember the Salesforce pitch, that spending 90% of your technology budget on maintaining systems of record was bad and that firms need to focus on front end services-based differentiators that are revenue builders, and not just back end infrastructure.

Data-driven insights gained from Salesforce have changed the

way both large and small sales and marketing teams drive revenue, shifting the CRM paradigm by creating an intelligence that was previously inaccessible using legacy systems. Salesforce did this by not only making the back-end infrastructure irrelevant, but through a great user experience, analytics, and customer service.

The need for accessible, actionable drug safety insight to drive departmental as well as overall commercial success in large and small biopharma companies shifts the PV software paradigm in the same way, albeit 18 years later.

What does the Salesforce of PV software look like?

Companies that specialize in back-end infrastructure like Oracle, ArisGlobal, and other cloud competitors will no doubt continue to iterate on the best ways to deliver the back-end infrastructure for PV. The emergence of artificial intelligence and advanced machine learning will continue to evolve how databases are constructed and maintained. The efficiencies created in case processing by these technologies provide an opportunity to have a long-term, trickle-down effect that will free up resources to accelerate aggregate insight generation from those cases.

The immediate opportunity for intelligence, however, is how data and analytics PV software can better interact not only with traditional sources like ICSR databases, FDA Adverse Event Reporting System (FAERS) data, VigiBase, and clinical trial data, but with emerging, disparate sources such as social media, claims, electronic health records (EHRs), and other unstructured data. Bringing these pools of information together creates an opportunity to enhance signaling algorithms, make validations and assessment more efficient, and ultimately get answers to drug safety questions faster.

However, in order to bring these data together, extensive ontologies need to be created to link all of the data. Drug name and active ingredient represented as national drug code (NDC), Rx concept unique identifier (RxCUI), or ICSR drugs need to be resolved to one record. Adverse event coding in MedDRA needs to be mapped back to verbatim labeling and ICD-10 codes. Drugs need to be characterized by anatomical therapeutic chemical (ATC) classifications, NDF-RT, label status, etc. This burden should not fall on the end user, the business, or IT within an organization. Next-generation PV software that will disrupt legacy vendors need to provide these ontologies and mappings off-the-shelf to be able to further drive immediate, actionable insight.

Arguably more important than how software interacts with the data, is how end users engage with software. Complicated, slow, and unintuitive software leads to a poor user experience. Legacy software and platforms that were built during web 1.0 will no longer be acceptable. And datamining in 2018 should not require an end user to be a data scientist. The platform that is able to shift the PV software paradigm will be one that reinvents how end users feel about the tools they use for their day-to-day jobs. Bottom line, a safety reviewer has to *want* to use and engage with the software, rather than see it as a burden. When this happens, PV software will shift from not only just a system of record, or just one of engagement, but truly a system of intelligence that was not previously capable with legacy platforms.

Summary

The market for PV software in 2018 and beyond is one that is attempting to catch up to other verticals that have long been disrupted by the "death of software." The barriers that were in place such as regulations with a moving target, drug safety's role as a cost center only, and the difficulty of accessing data are breaking down. The result is that there are now choices in the PV software market that weren't available just a few years ago, with potential clients that are more willing than ever to look past the systems of record and focus resources on building a system of intelligence that will drive PV workflow for years to come.

The market for PV software in 2018 and beyond is one that is attempting to catch up to other verticals that have long been disrupted by the "death of software."

Vendors focused on data and analytics can shift the paradigm of PV software and allow the science of PV to advance at a rapid pace. Innovation will come with end users empowered to take advantage of disparate data sources through a modern user experience. New signal detection algorithms and new, more efficient workflow built on the cloud and infinitely scalable, will allow drug safety departments to provide actionable contributions to all areas of an organization.

Although it is unlikely that mock demonstrators will be seen at any drug information or regulatory conferences, PV software is indeed having its "Salesforce" moment.

Reference

1. Dumouchel, W., 1999. https://amstat.tandfonline.com/doi/abs/10.1080/00031305.1999.10474456#.W_1jnZNKh0J

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Leveraging Technology to Develop New Trial Endpoints

Bill Byrom, PhD

Outlining the potential of three mHealth technology approaches in enabling novel and more robust clinical outcomes measurements.

American physicist and mathematician Freeman Dyson said that the year 2000 was essentially the point at which it became cheaper to collect information than to understand it. This observation, made almost 20 years ago, still rings true today as we consider the growing number of devices that we interact with on a daily basis and that collect all kinds of digital data.

This is particularly the case with our smartphones and the sensors contained in many everyday appliances that connect and deliver data through the internet of things (IoT). Modern smartphones contain sensors that were originally in place to enable certain handset functionality, but the data they generate are now being leveraged in other novel ways to add value to the user. For example, most of them contain an accelerometer sensor. This is used to understand the 3D spatial positioning of the device and to detect when the device is rotated to enable the screen display to switch between portrait and landscape modes. However, this is the same sensor used in many activity monitoring devices, such as Fitbit or Garmin wearable health trackers—and the same 3D accelerations generated and stored by the sensor to determine screen orientation can also be translated into activity parameters such as the number of steps taken by the user while carrying their smartphone. Most devices now contain health and wellness apps to exploit this capability and provide additional value to the user.

This interpretation of existing data for new purposes is an exciting area of innovation that we are seeing increasingly in the area of personal health and wellness, and it has huge potential to transform the way in which we capture measurements from patients in clinical trials. Simply put, technology like this is enabling us to provide richer insights and potentially measure new meaningful constructs that we have been unable to assess robustly in the past.

Perhaps most importantly, technology gives us the ability to think originally. The ways in which we are able to leverage existing technologies developed for other purposes, in new and novel ways, to collect insightful health status data from patients in clinical trials is an exciting area of current innovation. At the 2018 Drug Information Association (DIA) Annual Meeting in Boston, there were a number of presentations exploring this precise topic, which generated meaningful and enthusiastic conversation throughout the meeting. Ahead, I provide a brief review of the session that I chaired, entitled "Future of Endpoints," which discussed three diverse examples at different stages of maturity in terms of their potential application within clinical trials. I further discuss future directions for these approaches, and the kinds of activities needed to enable their ultimate use to support pharmaceutical and regulatory decision-making.

The aim of using technology in clinical trials is to simplify processes, make participation easier, improve quality, facilitate decision-making, and collect reliable, honest data. When collecting health outcomes, it is important to employ approaches that enable the optimal assessment of the study concepts of interest. In some cases, this may involve the use of a technology solution.

Three approaches that were presented in the DIA session are considered in this article. The first, presented by Alejandro Zamorano (PainQx) explored the use of modern brain-sensor headbands to measure electroencephalogram (EEG) signals and develop objective measures of pain. The second, presented by Christian Gossens (Roche) examined the development of new health outcome measures in Alzheimer's disease using smartphone sensors. The third, presented by myself, explored the use of motion-based gaming technology platforms to

develop new objective measures of movement and mobility.

Each approach shows promise in leveraging existing technology solutions in novel ways to deliver health outcomes measures that either provide a richer picture of health status due to the ability to measure remotely, or provide a potentially superior approach to development of sensitive, objective measures compared to current practice.

Use cases

Use Case 1: Leveraging wearable sensors to measure pain

Wearable devices that measure EEG brain activity have been used to enable interaction with gaming systems, develop applications to facilitate activity and communication in impaired patients, and to provide brain training applications in personal health and wellness.[1] Examples of the latter two include the "Mind Speller" application that enables textual and verbal communication using EEG brain signals from patients with reduced motor functioning;[2] and brain training applications to assist the management of anxiety and concentration by providing insight into types of brain activity using neurofeedback.[1]

Portable EEG headbands provide a means to collect this data remotely or without specialist equipment during clinic visits. These are typically worn on the forehead and collect signals using a series of dry electrodes to generate a continuous EEG trace, although some discrete cochlear devices are in development.[3] Examples include MUSE (InteraXon Inc., Toronto, Canada), Emotiv EPOC (Emotiv Inc.) and ZenZone (NeuroSky Inc.).

While we discuss later in this article the additional work needed to ensure the reliability, accuracy, and precision of data collected in this way, if the potential use in clinical trials is to be realized, PainQx have conducted significant work on the validation of outcome measures derived from EEG signal data to provide objective measures of pain. In his presentation, Zamorano provided an insightful review of their scientific work to date.[4]

Foundational to this work is the property that chronic pain appears to be associated with increased alpha and theta EEG signals during spontaneous EEG recording, and low amplitudes of event-related potential (ERP) when the patient is presented with various stimuli.[5] PainQx have developed algorithms to interpret EEG traces to describe the patient's pain state by mapping quantitative measures of electrical activity in different regions of the brain responsible for the sensation and perception of pain. By filtering out components not related to pain sensation or perception, this "Pain Matrix" provides an objective outcome measure to describe pain incidence and severity. Pertinent areas of EEG activity are isolated, identified, correlated, and weighted to produce an objective score describing the patient's pain state. This approach has been seen to correlate well with subjective measures of pain and to distinguish between high and low pain in chronic pain conditions.[1]

While self-perception of pain nature and severity is a critical element to assess pharmaceutical intervention effects, generally recorded using patient-reported outcome measures (PROMs), this objective measure derived from brain activity monitoring may be useful alongside these traditional PROMs. In particular, in addition to providing additional supportive data to PROM endpoints, EEG-derived outcome measures may provide additional supporting data, may enhance study qualification/screening activity, and may provide a convenient mechanism to evaluate the real-time effects and dose optimization of analgesic and narcotic drugs during treatment.

Measurement using portable EEG headsets opens the door to remote measurement, and convenient measurement in clinic. However, their use relies upon satisfactory reliability, accuracy, and precision of data collected in this way. Some factors for consideration include the reduced number of electrodes, the fact that electrodes connect to the skin in a dry state, that measurements using headbands predominantly represent activity from the frontal cortex, and that device firmware must be relied upon to adequately filter and interpret the signals received. Some of this data is becoming available for appraisal in the scientific literature, and some additional work is needed to assess the scientific acceptability of the approach.

Use Case 2: Leveraging smartphone sensors to enable frequent outcome assessment in remote settings

As described above, the sensors within smartphone handsets are already being used in the wellness industry to provide health and fitness applications. Smartphones are already used in clinical trials to collect electronic patient-reported outcomes (ePRO) data, and leveraging their sensors to collect other data through active performance tests is a novel approach to accumulating additional objective data remotely and conveniently. Christian Gossens, PhD, global head of digital biomarkers at Roche, also presented in the "Future of Endpoints" session and described new work underway in the development and validation of performance outcomes (PerfOs) aimed at studying multiple sclerosis (MS) patients and conducted by leveraging smartphone components and sensors. This work is presented within the Floodlight Open study, currently recruiting online.[6]

The study aims to measure a participant's ability to perform simple tasks using their smartphone with the aim of understanding the effects of MS on cognition, dexterity, and mobility. For example, the assessment of pinching action between thumb and finger is commonly assessed subjectively using clinician-reported outcomes such as within the Unified Parkinson's Disease Rating Scale (UPDRS). This assessment measures aspects of dexterity, muscle weakness, and control. The Floodlight app has gamified this test and presented it as a task where subjects use the same pinching action on the touchscreen to "squash" tomatoes between thumb and finger as they appear on screen. In addition, a drawing test where users are requested to draw along the outline of a figure of eight shapes is included to measure other aspects of dexterity, hand-eye coordination, and muscle control.

In addition to enabling objective measures of constructs that have previously been measured subjectively by the clinician, one key advantage of this approach is the ability to study health outcomes more frequently than can be achieved through regular clinic appointments. This has been illustrated previously by Gossens and colleagues in their work on smartphone-delivered tests in Parkinson's disease (PD). Detecting tremor, for example, using a simple test where the smartphone is balanced on the palm of the hand for 30 seconds and tremor-related movements are detected using the ac-

celerometer sensor has already shown promise in the understanding of tremor symptoms in PD.[7] This may significantly improve understanding of treatment effects, especially for symptoms that present intermittently or may suffer from poor recall properties.

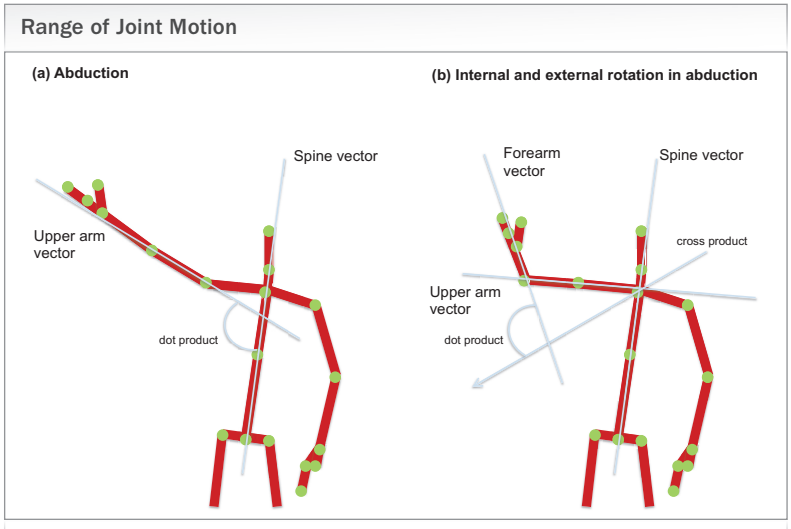
Use Case 3: Use of motion-based gaming platforms to measure movement/mobility outcomes

Motion-based gaming platforms use depth-cameras to detect body movements and enable users to interact with gaming applications in more immersive ways. The same depth-camera technology, and its associated software development kits (SDKs), can be used to develop custom software with application in education and health. The most commonly used solution is the Microsoft Kinect depth-camera associated with the Xbox gaming system, although other more advanced (yet similarly low-cost) technologies exist, such as the Intel RealSense camera range.[8] There are numerous applications utilizing this motion capture technology to study or encourage movement in healthcare, particularly in rehabilitation. Being able to track the 3D position and movement of body joints enables the assessment of movement, and the detection of correct exercising during rehabilitation. Jintronix, for example, have developed games using Microsoft Kinect to encourage adherence and engagement with rehabilitation regimens, which have shown good outcomes in terms of reduced readmission rates in orthopedic and stroke patients.[9] Similarly, being able to track facial landmarks enables the deployment of other health applications, such as rehabilitation systems for patients recovering from facial paralysis—for example, with Bell's palsy and stroke.[10]

Depth-camera solutions offer the potential to make objective in-clinic measurements that may previously only have been possible in more specialized motion laboratory settings or by using subjective clinician-reported outcomes (ClinROs). Simple range of motion, gait, and balance performance tests have been developed that leverage simple depth camera technology, both within and outside the context of a video game, some of which have shown reasonable performance in early validation studies.[11]

For example, converting the 3D coordinates of body joints into vectors representing the spatial orientation of parts of the body enables simple vector algebra to calculate the angles made between joints and thus provides an estimate of the range of joint motion (see Figure 1). Early validation work compared to goniometer measurements has shown promise for upper extremity range of motion measures for example.[12,13]

The use of motion-based gaming technology to develop movement-based outcome measures may enable the low-cost measurement of outcomes not possible outside specialist movement laboratories and may provide advantages over subjective ClinROs in providing measures that may be more sensitive, less prone to inter-rater variability, and capable of measuring more subtle aspects of movement and motion.



Source: Byrom

Figure 1. Estimation of range of motion using 3D joint coordinates.

Developing endpoints derived from novel use of technology applications

The ability to leverage endpoints derived from these novel approaches, and other approaches leveraging existing technologies in novel ways, relies upon the provision of evidence to support the use of the technology and to support the endpoint derived. Specifically, we must be assured that the device faithfully measures what is intended to an acceptable level of reliability, accuracy, and precision; and that endpoints derived are truly measuring a concept of interest of the study, are sensitive to detect changes in health status as a result of an intervention, and that meaningful change is understood. This is, of course, no different to the approach required to validate any measurement approach associated with any clinical endpoint used to measure intervention effects.

A comprehensive summary of requirements was published by the Critical Path Institute's ePRO consortium in the context of the use of wearables to develop endpoints to support regulatory decision-making and labelling claims.[14] These are summarized in Figure 2 on facing page, and also below.

A. Technology assessment

Usability and feasibility: Demonstration that the technology is usable within the target population and feasible within the context of the specific clinical trial.

Reliability: Data generated show satisfactory intra- and inter-device reliability.

Concurrent validity: Demonstration that the technology is truly measuring what is intended.

Responsiveness: Data generated are able to suitably distinguish changes when they occur.

B. Endpoint evaluation

Measures a concept of interest, as defined by the study protocol.

Content and construct validity: The endpoint provides a sufficiently comprehensive measure of a concept of interest that is

meaningful to patients and/or the treatment of their condition; and faithfully measures the construct intended.

Ability to detect change: Sensitive enough to detect change when a change exists.

Endpoint interpretability: The change in the endpoint deemed meaningful to patients is understood (e.g., minimally clinically important difference [MCID] or individual responder definition).

Conclusions

There is huge potential for thinking differently about how existing technologies can be repurposed to enable novel measurements for health outcomes and health status in patients. The increased insights obtained through more frequent home-based measurement, and new objective outcome data that was not possible before, enables sponsors to build a far richer and more insightful picture of intervention effects, which will aid early decision-making and contribute to labelling claims in the future. While these remain exploratory in nature and more work is needed to provide the level of validation around these new endpoints, they have great potential to aid drug development and regulatory decision-making, and may also have value in the care and management of patients in routine care.

The life sciences industry should adopt a culture of facilitating the exploration of new technology implementation within trials in an exploratory way, and aim to share experience, information, and access to the technologies showing most promise. Only through extended use will sufficient data and experience of using these new endpoints be accumulated to enable their acceptance in regulatory decision-making.

Endpoints Developed for Wearables

A. Technology evaluation		B. Endpoint evaluation
Evidence to support device selection	Evidence to support validity and reliability of selected device	Evidence to support derived clinical endpoint

• Safety
  • Performance and safety of the solution, as appropriate
• Suitability
  • It claims to measure a concept of interest as defined by the protocol
  • Usability and acceptability in the target patient population
  • Feasibility of use in the clinical trial protocol
  • Suitable solution characteristics (e.g. firmware control, 21 CFR part 11 compliance
	• Intra-device and inter-device reliability
	• Algorithm validation
	• Concurrent (criterion-related) validity
	• Responsiveness (ability to detect change)
		• Measures concept of interest
		• Content and construct validity
		• Responsiveness (ability to detect change)
		• Interpretability (responder definition)

Source: Byrom

Figure 2. Evidence to support clinical outcomes assessments derived from novel technology sensors.[14]

References

1. Byrom B, Mc Carthy M, Schueler P, Muehlhausen W. Brain Monitoring Devices in Neuroscience Clinical Research: The Potential of Remote Monitoring Using Sensors, Wearables, and Mobile Devices. Clinical Pharmacology and Therapeutics, 2018.
2. Katholic University of Leuven. Campus Insight Magazine. www.kuleuven.be/ci/28/28.pdf. (May 2010).
3. Looney, D.P. et al. The in-the-ear recording concept user-centered and wearable brain monitoring. IEEE Pulse 3(6), 32–42 (2012).
4. Prichep, L.S., John, E.R., Howard, B., Merkin, H., Hiesiger, E.M. Evaluation of the pain matrix using EEG source localization: a feasibility study. Pain Med. 12(8), 1241-8 (2011).
5. dos Santos Pinheiro, E.S. et al. Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. *PLoS ONE* 11(2): e0149085 (2016).
6. https://www.floodlightopen.com/en-US/
7. Lipsmeier F et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov Disord 2018; 33: 1287-1297.
8. Breedon, P., Byrom, B., Siena, L., Muehlhausen, W. Enhancing the Measurement of Clinical Outcomes Using Microsoft Kinect. International Conference on Interactive Technologies and Games (iTAG) 2016. *IEEE Xplore*. http://ieeexplore.ieee.org/document/7782516. (2016).
9. Jintronix. http://www.jintronix.com/wp-content/uploads/2016/07/TNJH-Case-Study.pdf
10. Breedon P et al. Face to face: An interactive facial exercise system for stroke patients with facial weakness. In (Rehabilitation: Innovations and Challenges in the Use of Virtual Reality Technologies; Eds: Wendy Powell, Albert "Skip" Rizzo, Paul M. Sharkey, Joav Merrick; Nova Science Publishers, 2017.
11. Breedon P, Byrom B, Siena L, Muehlhausen W. (2016) Enhancing the Measurement of Clinical Outcomes Using Microsoft Kinect. Interactive Technologies and Games (iTAG), 2016 International Conference on 2016 Oct 26 (pp. 61-69). https://doi.org/10.1109/iTAG.2016.17.
12. Byrom B, Walsh D, Muehlhausen W. New Approaches to Measuring Health Outcomes - Leveraging a Gaming Platform. Journal for Clinical Studies 2016; 8(6):40-42.
13. Lee SK et al. Measurement of shoulder range of motion in patients with adhesive capsulitis using a Kinect. PLOS ONE, 2015.
14. Byrom, B. et al. Selection of and Evidentiary Considerations for Wearable Devices and Their Measurements for Use in Regulatory Decision Making: Recommendations from the ePRO Consortium. *Value Health* (2018).

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The Ghost of Clinical Trials Past, Present, and Future

David Connelly, PhD

Have you seen many paradigm shifts lately?

How many times have you read about the urgent need to shift the clinical trial paradigm or claims that say that Wonder Tool X or Super System Y will do this for you? Have you ever attended a clinical trial "Innovation" or "Disruption" conference and left wondering in all the years the conference has been held, what has really been disrupted?

Clinical trials are deceptively complex, and many are becoming more sophisticated in their design and demanding in their conduct. It is clear there have been advances in many aspects of the ways we perform clinical trials, particularly the benefits brought by the application of technology and standards. There are also many initiatives and ideas, new technologies, and approaches being proposed. So, as we head toward the end of another year and approach the 2020s, are we confident we are on the right path to more effective and cheaper clinical development and clinical trials? Based on various publications, trade press, conferences, and similar, there seems to be widespread acknowledgment that doubts remain. There is anxiety, if not worse, some disillusionment.

Over many years in management, when faced with situations or information to review, I have learned to ask myself some simple questions. For example, why, so what, what can we do? I don't pretend to have all the answers, but when invited to consider this topic, I used this questioning approach. These are some personal thoughts and views.

Why are clinical trials so difficult and so much work?

Accepting that studies can be large and complex, have we, nevertheless, overcomplicated the problem? A clinical trial can be considered as basically a scientific experiment involving people. The clinical data generated from the subjects is key to determining the effectiveness and safety of the treatment. If this is the core data, then this means that all other data, and information, is ancillary.

Undoubtedly, this other data is important for many reasons: ensuring the study is well planned, managed, ethical, compliant, that the clinical data can be trusted, etc. Nonetheless, it does not determine efficacy or safety and so it can be considered ancillary.

If we accept this principle, then what are the implications? Have we structured organizations and developed and applied technologies that fail to appreciate that the clinical data is the core output of a clinical trial? Have boundaries been created in the wrong places and silos inadvertently created? We have many organizational groups managing different aspects of the clinical trial data. Clinical data is also spread across different systems and databases; it has become fragmented. When we try to integrate these often disparate systems, some never intended or designed to be integrated, the result is a patchwork of systems with inadequate interoperability and data all over the place. This is the so-called "Frankenstein" of siloed systems, so rightly highlighted earlier this year.[1] Despite the laudable efforts of many to move to industry data standards, we still end up mapping and reformatting data and meta data. The result is not only wasted time and a high maintenance cost, but a serious impediment to our ability to have critical clinical data aggregated and monitored in real time. Instead, it can be days and often weeks before it is available together for review and interpretation.

Have we built too much on legacy? We add new technologies on to old, and often just tweak underlying processes and SOPs. (We even tried to shoehorn the paper world of good clinical practice (GCP) regulations and guidelines into the mobile, digital world of the 21st century). If a great technology addresses one problem or

provides new capabilities, the unintended consequence can be rather than make things better, overall they get worse.

Over the last decade or so, management of clinical data has been driven down the commodity route, with off-shoring encouraged to save money. In some cases, job roles have been made narrower to allow for a more task-based approach with rapid training of less experienced resources. Nothing wrong with reducing costs, but with clinical trials becoming more sophisticated, the number of data sources increasing, and the types of data more complex, maybe this strategy needs to change. Surely we should be applying greater expertise and sophistication to derive valuable information from the data, and sooner? Clinical trial data is not an ancillary byproduct. It is the output of the clinical trial and arguably the whole purpose why the trial was conducted in the first place.

Sponsors take large risks, each spending millions, if not billions of dollars, on researching and developing new and better treatments or addressing unmet medical needs. Could those same sponsors spend or risk a little more on applying more innovation in the conduct and management of clinical trials? Do we as an industry prefer old, low-risk methods and systems that are tried and tested and are we too accepting of their limitations? The accusation is often made that the industry is too conservative. So what can we do to change this? By not investing more and driving change, are sponsors missing out on a tremendous opportunity to not only improve the efficiency of their operations but also on enhancing the value of their portfolio of R&D prospects? Should CROs be doing more, or are they indirectly held back trying to meet the requirements of their clients?

Consider that with many treatments becoming increasingly sophisticated, personalized, and "biological" (e.g. cell and gene therapy) could we be inadvertently failing or delaying in the application of modern technologies, such as live analytics and the use of artificial intelligence, that could help determine and more quickly prove the effectiveness and safety of new treatments? Is the boundary between controlled clinical trials and real-world evidence studies another unnecessary silo we have created, exacerbated by limitations of our technologies?

We still tend to focus on technology and systems separate from processes. Though there are indications in the market this is now changing, traditionally, clinical service vendors are also separate from clinical trial software vendors. So, looking back over the last two or three decades, how well has this worked? How modern, fit for the real world, and meeting the needs of its users are these systems and tools? Who believes we are at the forefront of all industries in applying modern technology and smart processes in clinical trials? Shouldn't we be at the forefront? After all, clinical trials may involve us genetically modifying live cells inside people. The reality is today we often don't know,

Purpose-Designed Path

Figure 1. Which makes the most sense? Integrate the old (legacy) and add on new technology, or start again and with fit for purpose?

from one week to the next, how these patients are responding to clinical trial treatments and assessments. Imagine if we didn't have sensors on passenger jet aircraft monitoring 1,001 aspects of the plane and providing information to the pilots and to maintenance on the ground. Instead, every few weeks we asked the pilot how the plane was flying, or asked did anything seem not right?[2]

So what?

There are many consequences for patients and their families (i.e., ourselves too), doctors, nurses, study coordinators, etc. at the investigator sites and for our industry.

The "insane cost of developing new drugs" when considering the high and late failure rate is well known,[3] so too the consequences, including potentially good or life-saving treatments remaining undeveloped. A third of all new marketed products are found to have serious safety issues not recognized before in the clinical trial data.[4] Surveys continue to report significant barriers in participating as a principal investigator (PI), while half of first-time investigators say never again[5,6]. Another consequence of the high cost of development is the very high price of many new treatments. Admittedly, clinical trials are only one component of the R&D cost, but, nevertheless, this cost is sizeable and a late-stage clinical trial failure or a wrong go/no-go decision can be disastrous. The high cost of new treatments leaves governments and healthcare payers reeling, struggling, or refusing to pay, while large pharma share prices have tended to stagnate with the response being many pharma companies have spent more on share buybacks and dividends than on R&D.[7] It isn't good business for the sponsor companies either.

Has the time come for the life sciences industry to truly learn from other industries? We are seeing mega large, global technol-

ogy companies move into selected areas of clinical research. This should be positive, but aren't the solutions to some of our challenges more fundamental?

What can we do?

In general terms, we can stop doing the same thing, and stop repeating the same mistakes. We should stand well back, look up, and ask ourselves: if we were to develop new methods and processes for designing, conducting, and managing clinical trials, and ensuring optimal patient safety, what would they look like? What are the outcomes we want to achieve? Even with blue sky thinking, the chances are most of it can be done today, or the right pieces put in place now to enable many advances, with the rest slotting in when ready/available.

- Have a real commitment to bring about change and allocate the resources, financial, and people.
- Build for flexibility and adaptability in a fast-changing world. One type of system or process probably doesn't fit all, not for all types of trials, all products, in all sites, in all geographies. It is like saying we only need one type of motor vehicle, or one type of car, to meet all our transport or recreational needs.
- Be brutal with legacy technology, organizational structures, job roles, and processes. Ask whose investment you are protecting?— yours or the vendors? Look at the vastly scalable modern technologies being used elsewhere, including in our daily lives, and accept no less.
- Be practical. For example, few people will argue that being able to have all sites enter or load clinical trial data into an electronic medical record (EMR) and then extract data from these systems looks like a more logical, streamlined approach that could save site staff work and potentially reduce errors. In specific studies, in certain situations and locations, this could be a great approach. As a scalable, viable solution within the next decade, this may be quite another matter. So, what can we do now?
- Treat clinical trial data as if it is as valuable as gold dust, not sand. Invest in the application of modern data science technologies and expertise, live analytics, and AI rather than commoditize data management.

We will also need a variety of software systems and tools to conduct and manage clinical trials. One system for everything is probably not realistic nor optimal. We obviously need speciality disciplines, experts, and organizational structures to support them. However, design boundaries in the right places and do not perpetuate legacy. Accept that clinical trial data is the core output of a study and place a boundary around this, not carve it up into silos within.

Why not have one purpose-designed system (or systems) with one database that can manage all the data for your clinical trial, rather than have separate systems and tools for eDC, ePRO, esource, lab, safety, econsent, reporting, analytics, etc. Avoid the Frankenstein of patch-worked systems, all with their own databases, management, and support systems, and all the costs, inefficiencies, and delays they cause—even when "integrated." Using one system, together with embedded workflow and communication tools commonly in use elsewhere, can unite rather than fragment clinical trial teams, allowing them to operate more easily as one team, including between sponsors, CROs, and sites.

Look carefully at the content and boundaries for the "ancillary" data. Is it any wonder that one of the favorite systems for clinical operations staff to complain about is the clinical trial management system (CTMS)? What does it actually do, or is it a legacy concept? Now we have electronic trial master file (eTMF) systems, trial supply logistics tools, investigator grant management tools, etc. Where should these boundaries be optimally drawn elsewhere? How do we want our teams to communicate and work?

Web portals designed to bring information from diverse sources and display, depending on the user needs and role, are a useful approach to overcoming the shortcomings of many separate systems and tools. However, they still require integration of many backend databases and can be complex and costly to set up and maintain. Why not avoid having so many separate systems and tools in the first place?

A modern smartphone can be a phone, a music player, a video player, a camera, a calculator, a diary, a computer, etc. It is not all those separate devices integrated. Why not have apps with all the functionality needed, communicating with a single platform around a single data repository, rather than all these separate systems?

A complete rework of our approach, technologies, and processes may seem scary, costly, and time-consuming. Indeed, possibly a distraction to developing new treatments. It needn't be, though. It needs a simplified, back-to-basics and sound principles approach. There are solutions and technologies that already exist that can sweep away the past and present, the Frankenstein's monsters and ghosts, and bring in a much brighter future. For those with courage, who ask the right questions, there is the opportunity to leave the rest way behind.

References

1. Streeter, James. "Eliminating Silos: Dismantling the Frankenstein of Clinical R&D." *Clinical Informatics News*, 2018
2. Griffiths, Andrew; Angus, James; Brown, Andy. "Revolutionizing Clinical Trials Through Real-Time Data Capture and Analytics." *Pharmaceutical Executive,* 2018
3. Herper, Matthew. "The Cost Of Developing Drugs Is Insane. That Paper That Says Otherwise Is Insanely Bad." *Forbes*, 2017
4. Downing NS; Shad ND; Aminawung JA; Pease AM; Zeitun JD Krumholz HM; Ross JS. "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010." *JAMA*, 2017 317(18):1854-1863
5. Corneli, Amy; Pierre, Christine; Hinley, Terry; Fordyce, Christopher; Hamre, Gerrit; Roe, Matthew. "One and Done: Reasons Principal Investigators conduct only one FDA-regulated drug trial. Contemporary *Clinical Trials Communications*, 2017 (6) 31-38
6. Mahmud A; Zalay O; Springer A; Arts K; Eisenhauer E. "Barriers to Participation in Clinical trials: A Physician Survey." *Current Oncology*, 2018 (119-125)
7. Lazonick, William; Hopkins, Matt; Jacobson, Ken; Erdem, Sakinc Mustafa; Tulum, Öner. "U.S. Pharma's Financialized Business Model. " Institute for new Economic Thinking, 2017

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Patients as Partners in the API Era

The availability of FHIR-based APIs enabling patients to access and use their healthcare data for multiple purposes has opened a door to an entirely new world of opportunities for partnering with patients on clinical studies

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In the world of regulated research, we're conditioned to do things the same way, over and over again, to conform with SOPs. With respect to clinical studies, patients are anonymous "subjects," and we're enslaved to the case report file (CRF), designing studies to collect a set of data entered into EDC systems and moved along a complex, often recursive chain through data management, analysis, and interpretation. It's not easy to exercise creativity in trials, because we can be punished severely if we stray from the tried-and-true path.

Historically, all this made sense, since medical records were generally in paper folders, stored in massive mechanical file systems. To make the data usable, we relied on coordinators to copy the data into the CRFs, recognizing the need to scrutinize every data point because of the likelihood of transcription or omission errors.

Even when electronic medical records (EMRs) became available at sites, there wasn't much of a change to the transcription process. In some cases, researchers learned to tap into an electronic health record (EHR) system for source data verification, and risk-based monitoring tempered the monitoring burden somewhat. But in research, it still all started and ended with the CRF. And it generally seemed easier to just copy the data into EDC, rather than confront the complex challenges of trying to load it in electronically from EHR systems.

But while research labors on, the world of digital healthcare has been transformed. The U.S. 21st Century Cures Act established a requirement for certified EHRs to allow patients to access their data "without special effort" and "without the requirement for vendor-specific interfaces" by 2019. This requirement has become realistically attainable with HL7® FHIR®.

As Don Rucker, National Coordinator for Health IT, noted in a Health Information Technology (ONC) blog, "Open and accessible APIs (application programming interfaces) have transformed many industries. We think they can transform healthcare as well." A more recent ONC blog from Steve Posnack has shown how healthcare is already poised to capitalize on the era of APIs. In his recent celebrated *New Yorker* article, Atul Gawande has identified targeted apps built on APIs as a critical tool to lessen the EHR burden on clinicians, by allowing medical staff to "pick and choose the apps according to their needs." And if this is happening in healthcare, why can't this be the case for subjects, investigators, and research professionals? The SMART on FHIR (Fast Healthcare Interoperability Resources) app store provides a tangible glimpse into what apps built on FHIR APIs could also do for research.

But while HL7 FHIR has made this possible, it still requires a committed effort to make it happen. Within the healthcare industry, the Argonaut Project paved a path for engaging multiple stakeholders (providers, IT vendors, and consultants) to work together on a common implementation guide for using patient-focused APIs. This approach has been repeated by the Da Vinci project, involving a similar collaboration of participants plus payers to use clinical data to support value-based care. Da Vinci has also taken a lead in implementing the FHIR Bulk Data capability to use APIs to access data for entire populations of patients—a use case that could be adapted to improve pharmacovigilance and other research use cases as well.

One significant example of how APIs can help to partner with patients is the NIH *All of Us* Research Program, formerly the Precision Medicine Initiative, which seeks to engage one million patients who will voluntarily share their health and genomic data with research. The *All of Us* technology platform is built upon SMART-on-FHIR APIs—an approach that could also reinvent the conduct of clinical studies. The Apple Health Records app is already bringing digital health data to the masses, and FDA's recently announced MyStudies app builds on Apple and FHIR to support the use of real-world evidence.

FHIR forefather Grahame Grieve refers to it as "the web, for healthcare." The world of clinical research now stands before a doorway paralleling the advent of the Worldwide Web more than 25 years ago.

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