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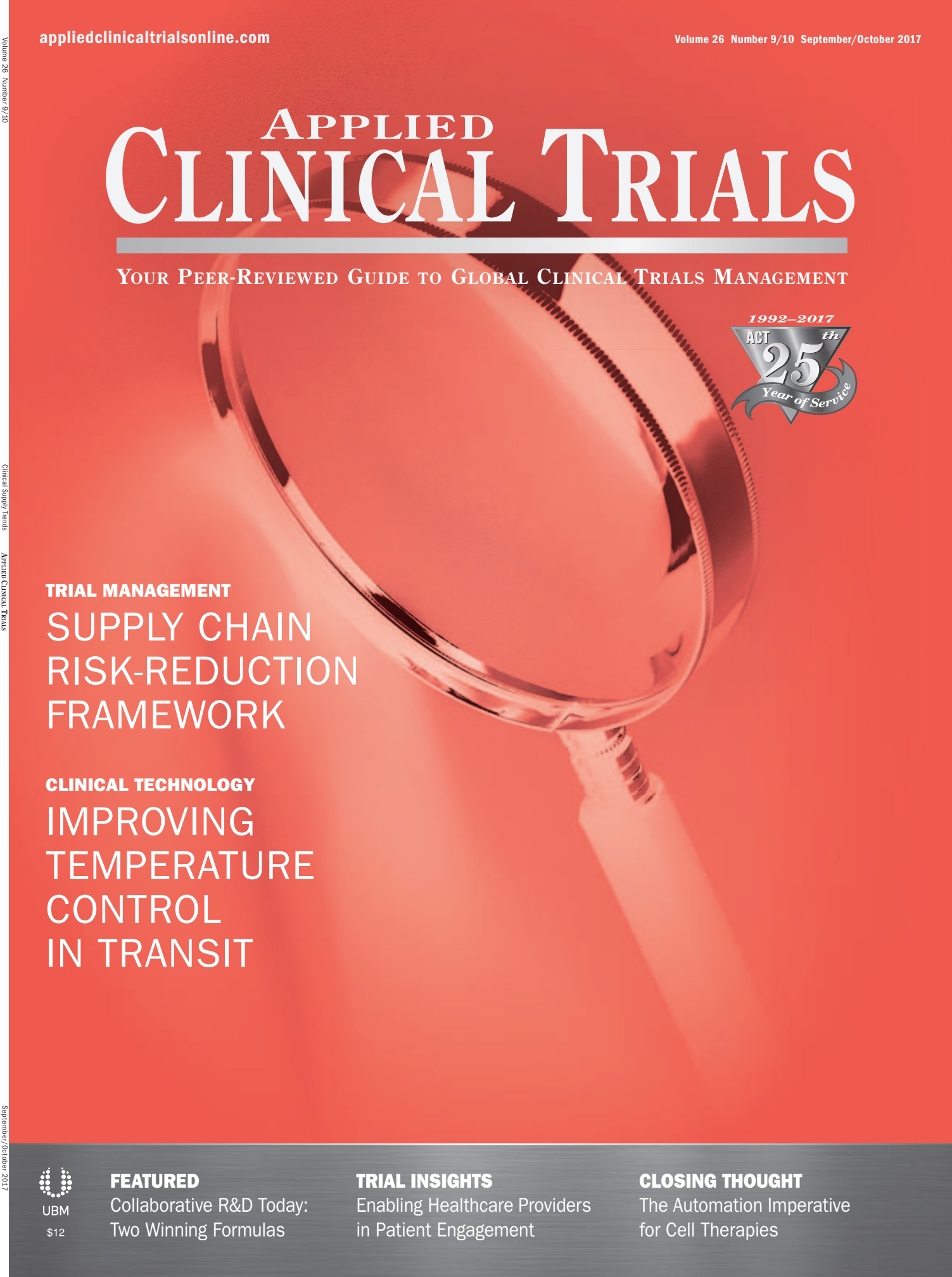

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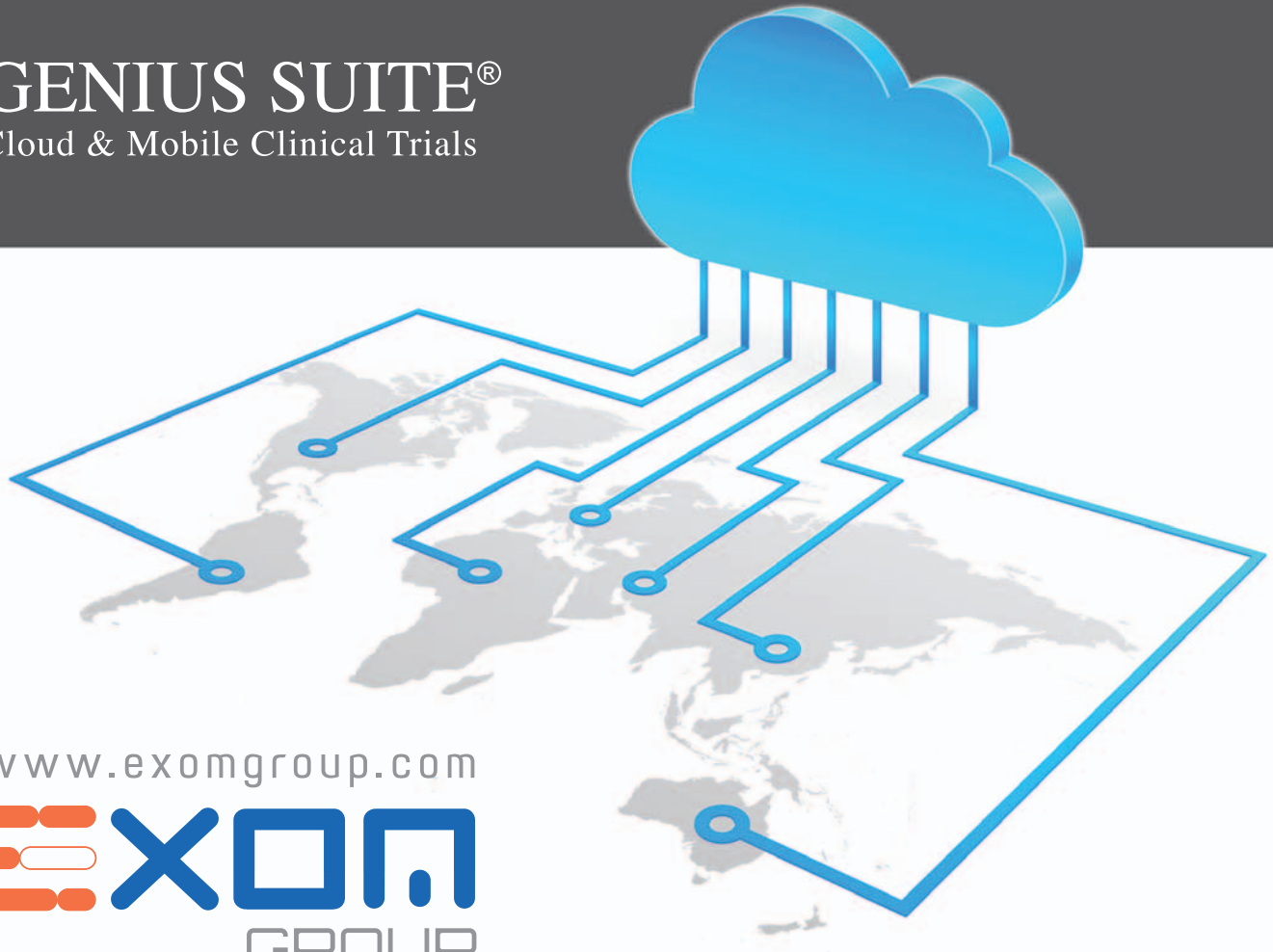

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Getting Onto the Cloud, One Step at a Time

LISA HENDERSON
Editor-in-Chief

In a new commercial from Perdue (chicken, not pharma), the "young-un's" walk around the farm with their older Dad, discussing chicken-farm management via tools in the cloud. When they say "cloud," their Dad looks up to the sky, then shakes his head.

We don't get that reaction so much anymore when we talk about eClinical technology in the cloud. Three years ago, cloud was a big topic fraught with anxiety around security. Now, it appears cloud technology is only limited by the resources a sponsor or CRO wants put into it.

You might think that those resources are related to costs or infrastructure required to move legacy systems to the cloud, and they are an issue for sure. But what I learned recently at the 2017 Veeva R&D Summit, is some companies still run trials on paper.

Ora Clinical, a specialty CRO focused on ophthalmology located outside of Boston, started moving its 100% paper processes into the cloud two years ago with Veeva's Vault eTMF solution. This was followed a year later with Vault Study Start-Up, and now the company is rolling out Vault CTMS. These were all processes that Ed Leftin, Senior Vice President, Technology, for Ora Clinical, felt were necessary for the company to provide real-time insight into trials, internal accountability, ability to measure and turnaround outcomes quickly for clients, and much more. The CRO is currently considering adding Veeva's EDC capabilities as a potential next module.

Leftin was not shy about sharing his experiences in implementing the Veeva cloud modules. His major takeaways and lessons learned were around change management and training. He noted the eTMF implementation was relatively painless. However, for the next two, he said he would've traded two weeks on implementation time for employee training (10 weeks and 12 weeks, respectively).

Leftin allows that his company is small—250 employees—but was cognizant of the benefits it would gain moving to the cloud. But to ensure there was no loss of time with employees inputting data into the new systems, Leftin says only new studies were rolled into the cloud.

Matt Wallach, President of Veeva Systems, shared at a media-biopharma roundtable that large pharmaceutical companies want to move to modern technology across all functional areas in the organization, but are overwhelmed with how to replace all of those legacy systems all at once. Wallach suggested that they do it in stages; for example, replace all the legacy applications with cloud solutions for just the new trials, then retire the legacy systems as those trials roll off.

It also appears from the experiences shared at the Summit that once one cloud system is successfully adopted in one functional area, people become comfortable and other areas follow suit. Veeva announced that its Adverse Event Tracking solution will be available in 2018. But Wallach said, "It will be like 2007 all over again. We will introduce another group of people to the cloud." In either scenario, legacy-to-cloud, or paper-to-cloud, learn from those who have gone before you in your company, or other companies. Don't underestimate the necessary training and happiness of your users.

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PEER REVIEWED

29 Mitigating Supply Chain Risk in Clinical Trials

Chad Presher, Adam Sheriff, Lorna Briddick

Outlining a decision-making framework that integrates real-world signals with supply planning methods to avoid potential interruptions.

PEER REVIEWED

NEWS AND ANALYSIS

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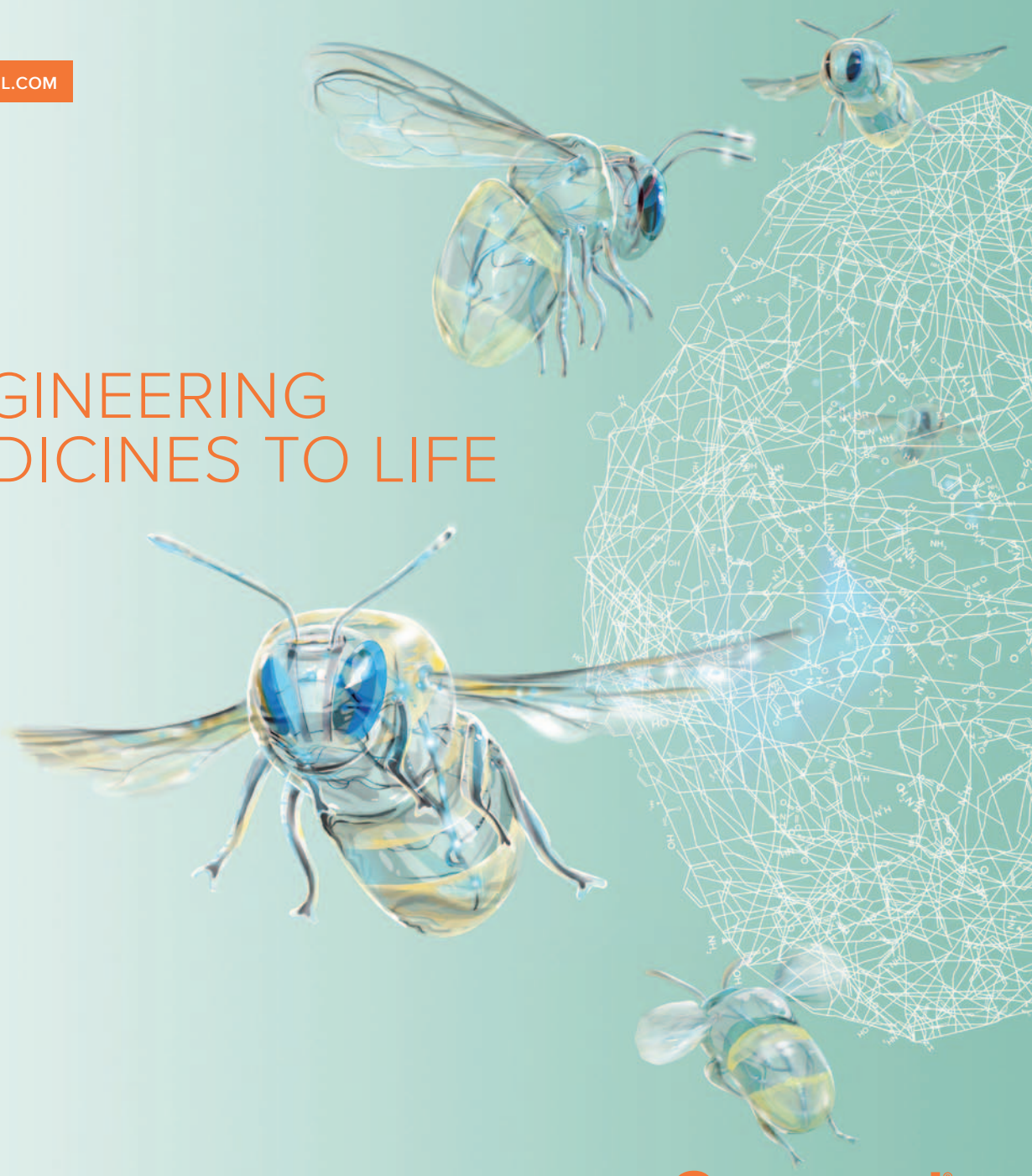

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Also available is ***Patient and Clinician Reported Outcomes in Clinical Trials***. This eBook features articles updating actual-use studies of ePRO in a large registry trial, as well as challenges, myths, and potential useful strategies associated with "Bring Your Own Device" (BYOD) adoption.
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SCORR Marketing and *Applied Clinical Trials* conducted an industry survey to find out what it takes to build strong partnerships and advance clinical research. The survey results are now available in this exclusive, 35-page special report.
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GLOBAL REPORT

EUROPE'S BATTLE TO HOST EMA POST-BREXIT INTENSIFIES

The Austrian capital, Vienna, has reportedly joined the growing list of frontrunners in the keenly contested race to secure the future head office of the European Medicines Agency (EMA) after the U.K. leaves the European Union (EU) in March 2019. Stockholm, Copenhagen, Amsterdam, Barcelona, and Milan are thought to be the other leading contenders, but a final decision is unlikely to be taken until November in a secret ballot of the EU Council of Ministers.

Austria's health minister Pamela Rendi-Wagner and Vienna's financial city councillor Renate Brauner presented their application to host the EMA in Brussels on Sept. 11, according to a report in the *Express*, the U.K. daily newspaper. The contest is now particularly fierce, with 19 cities, including Vienna, vying to become the new home of the EMA, it noted.

The EU Commission was set to examine all applications by the end of September, but according to diplomats, there will be no shortlist. The latest estimate suggests the cost of moving the EMA out of the U.K. will be around £521 million ($705 million), which is £163 million ($220 million) above the initial estimate, the *Express* stated.

"The EMA has calculated the cost of moving its operations and staff, and paying off the remainder of a locked-in lease that runs until June 2039, at more than half a billion pounds. Officials previously estimated it would run to £358 million," the report continued. "This figure includes £401 million to pay off the rest of the lease, £34 million to kit out its new home, £47.4 million for relocating the agency's 890 strong workforce, and £21.7 million on IT and audiovisual equipment and meeting rooms."

In 2015 alone, the EMA attracted 36,000 visitors, including scientists and health professionals, the report added.

Guidelines seen by *The Wall Street Journal* say the European Commission will assess bids on a series of strict criteria, including airport access and local schools, according to the *Express* report. Spanish health minister Dolors Montserrat set out the case for Barcelona to host the agency during a visit to Brussels in May.

"Barcelona is ready to host the EMA now. No one is offering a better combination of location, facilities, services, and a high quality of life from both a professional and social perspective than Barcelona," she said.

Going Dutch

Amsterdam was the early favorite to secure the EMA, according to a report published by *The Guardian* newspaper in August. In the Dutch application submitted to the European Commission, it said that losing the agency will prove a double blow to London when Brexit forces its move.

"The relocation of the agency will have considerable impact, not only because it has to move its headquarters and personnel, but also because the relationship with the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) will change and potential risks need to be minimized in the event of a hard Brexit," the document stated.

The MHRA enjoys a lucrative relationship with the EMA, for which it carries out between 20% and 30% of the vigilance and licensing work the agency is responsible for, the report noted. The Amsterdam bid says this could change after Brexit, and that the Netherlands is well-placed to provide an alternative.

"Brexit will not only result in the relocation of EMA to another EU member state, but also very likely in a dramatic reduction, or withdrawal, of the work of the MHRA and the Veterinary Medicines Department (VMD) in the assessment of medicinal products for human and veterinary use," the authors wrote. "The MHRA and VMD currently also provide various services to the agency, including scientific support and [small] research assignments, regulatory advice to EMA experts, and the uptake of unclaimed scientific procedures. The Dutch Medicines Evaluation Board is able to provide a similar level of service to EMA in the event of its relocation to the Netherlands."

According to *The Guardian*, a spokesman for the MHRA said it did not necessarily believe the work it currently carried out would be lost post-Brexit.

— Philip Ward

WASHINGTON REPORT

FDA MOVES TO BROADEN ACCEPTANCE OF REAL-WORLD EVIDENCE IN CLINICAL RESEARCH

The 21st Century Cures Act and the newly authorized prescription drug user fee agreement both aim to expand FDA acceptance of patient data from healthcare systems and observational studies in regulatory decision making. FDA, consequently, is working with stakeholders to better define and clarify the nature and sources of such real-world evidence (RWE) and how it differs, and converges with, information obtained from randomized controlled trials (RCTs). The aim is to use data from health plans and registries to answer questions about treatment effects and outcomes for broader patient populations than possible in a specialized research environment, and, in the process, to streamline clinical development and inform the safe and effective use of medical products.

The Cures Act supports FDA use of RWE to evaluate additional indications to an approved therapy and safety and effectiveness after a product comes to market. Notably, the legislation stops short of mandating FDA consideration of this evidence in assessing new medical products, as sought by some reformers; FDA retains authority to require RCTs for product approval and postapproval studies. To implement the RWE policy, FDA has two years to develop a framework for assessing information sources and to set standards and methodologies for data collection and analysis.

Similar initiatives for advancing the use of RWE in FDA policies and approval decisions are included in the goals letter implemented by the latest version of the Prescription Drug User Fee Act (PDUFA VI). The program seeks to expand the capacity of FDA's Sentinel Initiative to help assess drug efficacy as well as safety. FDA will hold public workshops and propose pilot studies or methodology projects to address concerns and challenges related to RWE use, and additional guidance will clarify the use of such evidence to support decisions on supplemental indications and postmarketing commitments.

A preview of how FDA may address these issues can be seen in a final guidance published August 30 on the use of RWE to support regulatory decisions for medical devices. The document finalizes a draft guidance issued in July 2016 and aims to encourage the development and use of evidence gleaned from actual product use to help bring new devices to market faster and based on more reliable information.

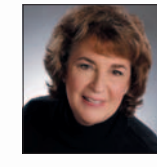
Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), and CDER colleagues anticipate that broader use of "big data" from electronic health records, claims data bases, social media, and "smart" devices can support and streamline the current clinical development process. Writing in *the Journal of the American Medical Association* (JAMA, 2017; 318(8); 708-709), the authors explain how RWE may facilitate clinical research by aiding in trial design, study site selection, external control group formation, and study enrichment. While FDA has utilized RWE primarily to assess drug safety issues, Woodcock and staff envision that it such information will be useful in evaluating drugs for rare diseases where a randomized study is not feasible, in developing natural histories of certain diseases, in devising optimal dosing regimens, and in assessing longer-term outcomes unknown at time of new drug approval.

Experts weigh in

In its Work Plan for implementing Cures issued in June, FDA outlines its intent to develop the framework for evaluating potential uses of RWE. FDA launched the project at a public workshop Sept. 13, where participants discussed the definition of real-world "data" (RWD)— information related to routine health delivery —vs. real-world "evidence" that addresses the benefits or risks of a drug derived from RWD analysis. Presentations focused on challenges involved in RWD collection and quality, innovative methods for developing RWE from RWD, and promising areas for RWE pilot demonstrations.

To encourage broader consideration of these issues by the medical community, an FDA collaborative center led by Yale University and the Mayo Clinic outlined approaches for combining evidence from observational studies and RCTs in a recent webinar on utilizing RWE "beyond randomized controlled trials."

FDA also has engaged the National Academies of Sciences, Engineering, and Medicine (NASEM) Forum on Drug Discovery, Development, and Translation to host three workshops on the impact of RWE on medical product development and on health product payment and delivery. The first session Sept. 19-20 addressed incentives for collecting and using RWE and gaps in data generation. FDA officials and experts from industry, academia, healthcare systems, and patient organizations examined the value of RWE in research studies, among other topics.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

9/15/17: Utilizing Animal Studies to Evaluate Organ Preservation Devices (draft)

9/15/17: Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Human Papillomaviruses

9/12/17: Evaluation of Age-, Race-, and Ethnicity-Specific Data in Medical Device Studies

9/1/17: Providing Regulatory Submissions in Electronic Format—Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling (draft)

8/31/17: Use of Real-World Evidence to Support Regulatory Decision-Making for Devices

The following committee meetings are scheduled for October:

- Cellular, Tissue and Gene Therapies Advisory Committee ***Oct. 12***
- Patient Engagement Advisory Committee Meeting ***Oct. 11-12***
- Vaccines and Related Biological Products Advisory Committee ***Oct. 4***

EU REPORT

VALPROATE RAISES QUESTIONS AGAIN ABOUT THE QUALITY OF EUROPEAN DRUG REGULATION

Have the regulatory authorities in Europe dropped the ball again? After the Mediator debacle a decade ago, in which thousands of patients were exposed to dangerous adverse effects, European rules on drug safety monitoring were tightened up and the watchword was "never again." But now the teratogenic effects of sodium valproate are being revealed in all their appalling severity and scale—50 years after its launch, and in a chilling echo of the thalidomide tragedy that was the genesis of modern drug regulation more than half a century ago. The European Medicines Agency (EMA) hosted a public hearing on Sept. 26 as part of a new review of valproate use. The agency is considering whether to restrict use of valproate-containing medicines by women of childbearing age more severely than it already did in 2014.

Did patients know?

The warnings and restrictions then were designed to ensure that patients were aware of the risks of malformations and developmental problems in babies who are exposed to valproate in the womb. But plenty of evidence, anecdotal and systematic, suggests that many patients were not made aware. EMA admits that "concerns have been raised about how effective the measures have been in increasing awareness and reducing valproate use appropriately in its various indications." In France, in particular, where a class action is now underway against Sanofi, the principal manufacturer there, the national medicines regulator has asked EMA to consider whether further EU-wide action should be recommended.

The agency's pharmacovigilance risk assessment committee is examining the available evidence and consulting with stakeholders. Nearly 100 members of the public applied to take part in the September hearing, to talk about their experiences with valproate.

Long history of questions

This episode has, at first sight, all the appearance of a gigantic error by regulators. The risks associated with valproate in pregnancy have been well known for years, with early questions raised as far back as the 1980s.

In 2006, the U.K.'s National Institute for Health and Care Excellence (NICE) said, while assessing Abbott's version of the drug, Depakote, that it should not be routinely prescribed for women with child-bearing potential. Already then, studies were suggesting that many doctors and patients were not aware of the risks related to its use. Over the following years, concerns proliferated in a range of published studies, and by 2011, NICE was having to defend itself against accusations that its evaluation of the drug was ignoring the risks. In 2015, the U.K.'s medicines agency urged healthcare professionals to give better information to women about the risks, and in France, where 80,000 women were taking the drug, the national agency limited valproate prescribing to specialists. As anxieties mounted and lawsuits started to fly, the French health minister instigated an inquiry into whether sufficient warnings had been given by doctors.

By early 2016, the state investigators concluded that the health authorities and drug firms in France had shown "a lack of responsiveness" about the need to provide adequate patient information. Sanofi said that it had "always been proactive" on the subject and had respected its "obligations to inform health professionals and patients," and had asked the authorities to update product information as far back as 2003. But for generic versions, leaflets and product information summaries were updated only in mid-2015—and elsewhere in Europe, other authorities were also accused of displaying "a degree of inertia."

Answers needed

So what has gone wrong? Have regulators not acted with sufficient energy? Have drug firms been slow to modify their drug information? Have prescribing physicians not taken account of advice to act with caution, or to inform patients of risks? Or have patients not listened, or not understood? It is not, of course, quite so simple. For all its hazards, there are cases in which valproate is the only drug which can adequately control bipolar disease or epilepsy. EMA states in its invitation to the September hearing that "sometimes there may be no alternative to using valproate." The risks of dropping treatment before or during pregnancy also have to be weighed against the risks of fetal damage. And the incidence of adverse effects is not universal: valproate has been shown only to increase the risks significantly. Defenders of valproate point out that uncontrolled epilepsy also poses a risk for both the fetus and the mother, and claim that switching treatments once the patient is pregnant can also carry risks.

Nevertheless, across Europe there are now hundreds, even thousands, of parents of children with developmental problems, and they are now complaining vociferously that mothers were unaware of the risks when they took valproate. The questions raised by investigations now underway go much wider than the specifics of valproate. They need to cover a range of issues relating to information to patients, communication between regulatory authorities and prescribers, and regulatory focus at national and European levels when signals accumulate about risk.

**** EMA selective so far on PRIME acceptance. Read online at http://www.appliedclinicaltrialsonline.com/view-brussels***

— Peter O'Donnell

EMA NOTES

REPORTING SIDE EFFECTS OF DRUGS: The European Medicines Agency (EMA) has launched a survey to better understand patients' and healthcare professionals' awareness of reporting adverse drug reactions, including for medicines under "additional monitoring." It will be open for responses until Oct. 9. Take the survey here: bit.ly/2gGNckk

TAILORING DEVELOPMENT FOR OLDER PEOPLE: The EMA is inviting comments from the public on a reflection paper on how drug developers can better address the needs of older people who take medicines. In general, older people are the highest users of medicines. The deadline for comments is Jan. 31. View the report here: bit.ly/2fAajJE

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Q&A

THE EMERGENCE OF THE PATIENT-CENTRIC SUPPLY CHAIN

Research Triangle Park, N.C.-based Marken is a clinical trial logistics company involved in direct-to-patient services and biological sample shipments. Offering a GMP compliant depot network and logistic hubs in 45 locations worldwide, Marken is described as "the only patient-centric supply chain organization 100% dedicated to the pharma and life sciences industries."

Ahead, Marken CEO Wes Wheeler discusses the evolution of the patient-centric supply chain and how it is set to impact the clinical trials landscape.

Q: What defines the patient-centric supply chain?

WHEELER: I think the best way of describing a patient-centric supply chain is that it is one that respects the life-saving nature of what we do, and respects the fact that we're not just moving boxes, we're moving a biologic sample, an organ, a life-saving drug, or a life-saving vaccine, and that we realize that there is a patient behind every single one of those shipments.

Every protocol is different and every protocol requires a patient's informed consent. When the patient consents to a study, they're basically putting their personal data at risk, and they're trusting that the sponsor company or the CRO will protect the privacy of the patient and all of their health data. They're consenting to giving that data to a group of people they don't know. So there is the concern, with direct-to-patient studies especially, that patient data that can cross country borders could end up in the wrong hands.

We've taken this really seriously. In the last three to four years, we've developed a direct-to-patient to program, which is now extending into the cell and gene area, where we respect the fact that every protocol has an informed consent signed by a patient and that we're entrusted to protect their data.

Q: What are the key challenges associated with a patient-centric supply chain?

WHEELER: Data security and data privacy are the biggest challenges, when, for example, patients agree to a home-based trial or a personalized immunotherapy trial where their personal information is exposed. It's not like the old days when you had thousands of patients in a diabetes study and the potential for an individual patient's data to end up in the wrong place was minimized. We're now talking about highly personal transactions.

We go to a patient's home and deliver a drug, meet with a nurse, and the nurse administers the drug and maybe takes a blood sample and puts that back into the supply chain. That exposes the patient's name, potentially, and so we've developed processes and procedures to ensure that all patient data is blinded in our systems, that whatever data that crosses country boundaries is encrypted, and that it's not possible for the investigator to know what drug he or she is giving to the patient. Otherwise, you are compromising the integrity of the trial.

Q: How are digital and AI technologies impacting the patient-centric supply chain?

WHEELER: I'm not sure that we are being inundated by AI technologies yet on the clinical side, but on the digital side our biggest challenge will be dealing with wearable devices, point-of-care devices. I think ultimately the use of blood as the currency for clinical trials will diminish. It will be easier to transfer a patient's health and vital signs through a wearable device like a Fitbit, one that might be enhanced for the clinical trial to extract the patient's pulse, blood pressure, and perhaps blood content, temperature information, maybe even biomarker data.

When wearable devices replace the use of blood for testing, all that data will transfer to the Internet, and so can be compromised. That's where we have to be very careful. In the future, we will potentially be delivering wearable devices, making sure they're calibrated properly, making sure that they are transmitted under the appropriate conditions, etc., in addition to whatever blood we draw.

Q: How does social media/digital engagement feature as part of the patient-centric supply chain?

Wes Wheeler

WHEELER: We are working with many companies now and have around 100 trials ongoing with a direct-to-patient feature. These are very personal transactions. A patient could be critically ill with cancer and not able to make it to the doctor's office for treatment. We work on a training module for the drivers and we assign a project manager, who is responsible for setting up the trial, ensuring that the drivers are certified, and that the protocols are reviewed in detail. We get to know the patient by name, we can call the driver on his or her way over to the patient's home, and we make sure the nurse is there at the same time. The nurse does his or her work, drawing and centrifuging the blood, puts it into tubes, into the box, and the driver takes it to the central lab.

What we're working now, however, to make that process even better is an Uber-like technology. We hope to have this in pilot trials soon. It will offer the patient an Uber experience: they can go to their app, call up for a delivery, they can see which driver has been assigned and where the driver currently is. They can communicate with the driver, whether by phone or text message, and create that personalized experience.

Q: How do you see this approach evolving in the next two or three years?

WHEELER: I think right now every pharma company has got the message. There are some that are far ahead of others. I think in two years' time, every single significant clinical trial will offer patients the opportunity to take part from their home. This will grow, for example, in studies with Alzheimer's patients, Parkinson's patients, epilepsy patients, and terminal cancer patients, who perhaps cannot drive, cannot get to the doctor's office in time. The direct-to-patient approach will greatly increase retention and compli-

Q&A

ance among these patients, and enhance the experience for them. I think eventually that 10-20% of all patients will be treated at home.

Q: What emerging trends are you seeing?

WHEELER: The clear trend we see, which fits into our strategy, is that almost 50% of all trials in development right now are cancer-related, most cancer drugs are sterile, and about half of those drugs are biologically derived, requiring very sensitive handling. But the more exciting thing is the advent of cell and gene therapies, or immunotherapies. In autologous drug trials, where each patient's tissue is used to create a drug, each treatment is personalized. There are many of these trials being developed now and we're working with three major pharma companies as an exclusive supplier of cell and gene therapy supply chain work.

This is going to completely change the industry because every treatment is personalized, and requires an individual patient's tissue to be transformed into a drug within a certain timeframe and under certain temperature conditions. It means the traditional model of making bulk product in a factory for distribution to warehouses and wholesalers will go away. We will have banks of small pharmaceutical storage areas in retail pharmacies to store a patient's individual therapy, so when they're ready for the next treatment, they can go to the pharmacy and they get their own personalized medicine. The system we see with the Walgreens, the McKessons and the Cardinal Healths of this world currently storing hundreds of millions of drugs in tablets and bottles will go away, and we will move toward small vials of sterile product that are personalized with the patient's name on it.

Q: Is pharma prepared for this transformation?

WHEELER: Yes and no. I see a few companies that are very bullish and working hard at this, but the majority of this work is coming through small biotechs. They're not able to manufacture the stuff outside, they can't outsource to a [contract manufacturing organization], for example, so they're developing their own laboratories.

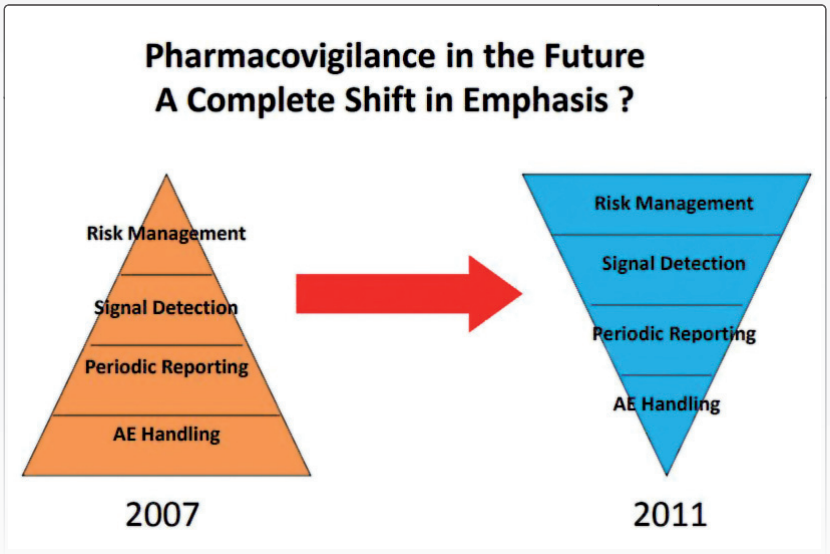
There's a whole cottage industry being formed, with small companies now advertising that they can do contract manufacture of cell and gene therapies. You are going to see a whole industry created around this.

— Julian Upton, European and Online Editor, Pharmaceutical Executive

LIFECYCLE MANAGEMENT

THE SHIFTING PERSPECTIVES ON PHARMACOVIGILANCE IN EUROPE

PV experts face new challenges as focus in field moves toward acting on real-world evidence insights



The European CRO Federation, or EUCROF, recently posted *Pharmacovigilance in 2020: Boldly Shaping the Future* (view: http://bit.ly/2xdXGPq), developed by its Pharmacovigilance Working Group. The aim of the paper is to offer insight into the increasing challenges of pharmacovigilance (PV) in the European Union (EU), and its effect on those professionals in this space. This paper is the first in a planned series, and the information in the report was gleaned from various sources, including conferences and publications, the European Medicines Agency (EMA), institutional websites, Medline, and from industry and contract research organizations (CRO) experience.

The authors lay out the fact that "the concept of the 'benefit/risk' ratio (no longer called 'risk/benefit,' which itself is a significant change) has become the common denominator not only of PV, but also of practically all drug-related regulatory activities throughout the lifecycle of a medicine, from preclinical to postmarketing." They agree that this is a sound approach, and in line with current clinical practice, but also state it's made PV activities significantly more complex, "since it implies that all benefit and risk data about a drug have to be put in context before any decision can be made on how to proceed."

The authors maintain that, amid the broader concept of real-world effectiveness, PV experts have to become benefit experts, capable of analyzing complex data from different sources with highly variable quality.

According to the report, the EMA is shifting perspective on PV from an "event-based" approach (i.e., making sure that all necessary data were collected properly and in a timely manner) to an emphasis instead being placed on what could be done with the available information.

The authors say, "....activities such as signal detection and signal management, along with risk management plans (RMPs) have become core pharmacovigilance activities. RMPs are a clear example of "proactive PV," since they give great importance not only to managing risk, but also to what we do not know about a medicine and to what can be done to minimize the possible consequences and/or to fill knowledge gaps.

The report, of course, is focused on the EU, and the authors concede that an examination beyond those borders is beyond the scope of the report. However, they do list specific examples of other countries that are requiring RMPs, and others developing legislation and regulatory guidance inspired by the EMA's good pharmacovigilance practices (GPVs).

With the increased challenges, EUCROF PV Working Group also advises that the use of an outsourcer specializing in PV could benefit sponsors.

PV is also going to have to become even more cross-functional, playing an increasingly important role across the lifecycle of a drug. This implies that all processes and procedures should be periodically reevaluated for adequacy and, if needed, improved, modified, or altogether substituted.

The common denominator for this re-evaluation should be the adoption of a proactive safety approach integrated as much as possible on top and across departments/divisions, but with provisions to include also affiliates and partners/vendors.

If these challenges are met, PV will allow marketing authorization holders not only to be compliant with existing and future regulations (no small feat in itself), but also to gain a competitive edge.

As stated earlier, all the present requirements, and the certainty that the situation will become more and more complex in the future, are probably "too much for one person" and possibly also "too much for a single group," with the possible exception of the largest companies.

This complexity has led to a growth in outsourcing of PV-related services. For most companies, delegating (wholly or in part) PV activities to organizations with specialist knowledge and expertise will become the most cost-effective solution.

— The EUCROF Pharmacovigilance Working Group

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REGULATORY

NEW RULES FOR EUROPEAN INVESTIGATIONAL MEDICINES

Gaps in the good manufacturing practice (GMP) controls on medicines for clinical trials are targeted in new rules from the European Union.

A new regulation setting out GMP for investigational medicinal products (view: http://bit.ly/2wy3z5z) was set to enter into force on Oct. 9, but national authorities in the EU member states will have until April 2018 to modify their national legislation accordingly.

"Good manufacturing practice for investigational medicinal products (IMPs) for human use ensures that there is consistency between batches of the same IMP used in the same or different clinical trials, and that changes during the development of an IMP are adequately documented and justified," it says.

The new measure has been issued in parallel to an update of GMP rules for authorized products, but it goes further in many respects, because, as its introduction says, in this area "there are no fixed routines, there is a variety of clinical trial designs and, consequently, packaging designs. The toxicity, potency, and sensitizing potential of IMPs for human use may not be fully understood at the time of the trial. Because of this complexity, the manufacturing operations should be subject to a highly effective pharmaceutical quality system."

Manufacturers will be obliged to meet similar requirements as manufacturers of authorized products on GMP requirements such as personnel, premises, documentation, and procedures. But there is an emphasis on the need for close cooperation between manufacturer and sponsor, particularly in sharing inspection reports and information on quality issues. The importance of documentation is also stressed, to allowing tracing of the history of the manufacture of each batch and any changes introduced during development.

There are additional requirements for retention of samples. Samples of each batch of bulk formulated product, key packaging components, and each finished batch will have to be retained for "at least two years after the completion or discontinuation of the last clinical trial in which the batch was used." And for advanced therapy IMPs, GMP provisions should be adapted "in accordance with a risk-based approach."

Detailed requirements for inspections also feature prominently. "Provisions on inspections by the competent authorities of the member states should be established," says the new rule. For third-country manufacturers of IMPs, inspection frequency should follow a risk-based approach. Common standards and procedures for GMP inspections for IMPs "should be developed," and inspectors should be given adequate powers to conduct inspections. National authorities are to cooperate with each other and with the European Medicines Agency (EMA), sharing information on inspections planned and conducted. And the conclusions reached in an inspection report in any member state or non-EU country—whether positive or negative—will be valid throughout the EU.

— Peter O'Donnell

CLINICAL TECHNOLOGY

SURVEY: CLINICAL DATA MANAGEMENT DELAYS ARE SLOWING TRIAL COMPLETION

One of the largest, most in-depth surveys of clinical data management professionals shows that the time it takes companies to design and release clinical study databases is having a negative impact on conducting and completing trials.

According to the 2017 eClinical Landscape Study from Tufts Center for the Study of Drug Development (CSDD) and Veeva, it takes companies an average of 68 days to build and release a clinical study database. Delays in releasing the study database are associated with an increase of nearly a month downstream for other data management processes such as patient data entry and time to lock the database at the end of the study. Respondents that deliver the database after first patient, first visit (FPFV), take nearly twice as long to enter patient data throughout the study and about 75% longer to lock the study database when compared to those that deliver the final database before FPFV.

Electronic data capture (EDC) is the most widely adopted clinical application, used by all respondents (100%), followed by randomization and trial supply management (77%), electronic master file (70%), and safety (70%) systems. A majority (58%) of respondents use either Medidata Rave or Oracle Inform as their primary EDC system.

When asked about the type of data managed in their EDC, 100% of contract research organizations (CROs) and sponsors cite electronic case report form (eCRF) data, followed by local lab and quality of life data (60% each). However, respondents say eCRF data is the highest volume of data they manage in their EDC system (at an average of 78% of the total data managed). The next highest data volumes reported are central lab data and local lab data at 5% each. Remaining data types reported are each 4% or less. This demonstrates the need for processes and systems to support the industry's vision to have complete study data in their EDC.

More than three-quarters (77%) say they have issues loading data into their EDC application and most (66%) say EDC system or integration issues are the primary reasons they are unable to load study data.

The survey finds several common causes for clinical database build delays. Protocol changes is cited most by 45% of respondents, underscoring the challenge data management professionals have in dealing with changes as they are finalizing the clinical trial database for the start of the trial. This highlights the need to optimize the database design process with standards and systems that support more flexible design and rapid development.

Initial database delays also have significant downstream impacts on the time it takes sites to enter patient data in the EDC throughout the trial, as well as the final lock of the database once the study is complete. It takes on average five days from patient visit to when the data is entered into the EDC for companies that release the database before FPFV. When the database is released after FPFV, data entry time doubles to 10 days.

— Wire Report

REGULATORY

EFPIA REPORT PINPOINTS RISKS FROM EMA RELOCATION

A new 25-page report commissioned by the European Federation of Pharmaceutical Industries and Associations (EFPIA) has highlighted the serious risks posed to public health by the relocation of the European Medicines Agency (EMA). The relocation will restrict the agency's ability to call on and manage the network of expertise it relies on and limit staff retention and capacity, warn the authors.

Compiled by consulting firm Charles Rivers Associates, the study analyzes the range of activities undertaken by the EMA and considers the impact of the move on continuity, patients, and approval of new medicines.

The report identifies two key areas—the evaluation of applications for marketing authorization (MA) and monitoring the safety of medicines across their lifecycle—as having the most significant detrimental effect on public health due to the relocation.

Delays in evaluating applications for MA mean delays in access to new medicines for patients across Europe, while disruption to critical safety functions can lead to delays in identification, management, and communication of safety issues, thereby putting patients at risk, according to the authors.

Disruption to some activities could have knock-on effects on other activities, the report states. This is the case, for example, for pediatric departments, because of the role of the pediatric investigation plan (PIP) in MA, and disruption of which may impact the MA process. Additionally, according to the authors, the workload in some departments may increase as a result of Brexit, such as MA variations or a requirement for new site inspections, which also have implications on business continuity.

Transitional arrangements must be put in place to ensure the EMA has the time to manage the relocation and safeguard public health, they stated.

"The EMA plays a key role in Europe's health, ensuring that medicines are safe, effective, and of high quality," noted EFPIA Director General Nathalie Moll. "This report underlines the importance of both the location decision and transitional arrangements to the agency's future. Supporting the continuity of its critical functions, its ability to retain staff and access expert networks is central to its future and to public health."

To download a copy of the report, visit: http://bit.ly/2xYc5OJ

— Philip Ward

WOMEN'S HEALTH

EXPLORING STRATEGIES FOR TESTING MEDICAL PRODUCTS ON PREGNANT WOMEN

Under a provision of the 21st Century Cures Act approved by Congress last December, the National Institutes of Health (NIH) has launched a process for identifying policies and strategies likely to encourage more research on safe and effective therapies for pregnant and lactating women, including the ethical issues related to enrolling such patients in clinical trials. About half of some six million pregnant women in the U.S. take at least one medication, even though few drugs are specifically studied and approved for use during pregnancy and for nursing mothers.

The Cures legislation instructs NIH's Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHHD) to establish a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) with the aim of advising the research and drug development community on how to obtain reliable evidence in this area (view: http://bit.ly/2fRrhH4). Officials from leading federal health agencies, including FDA's Office of Women's Health (OWH), held an initial meeting Aug. 21-22, to examine the current state of research and key issues involved in establishing the task force and its work plan. The aim is to develop recommendations for regulators, researchers, health professionals and industry on how to obtain needed information on safe and effective medicines for women during pregnancy and after delivery.

The task force will examine how these issues relate to a full range of medical therapies, including vaccines, dietary supplements, and prescription drugs, in assessing what information stakeholders feel is important to be included in product labels. There is interest in exploring how approaches differ for existing therapies vs. drugs in development and to better understand what data is already available, common terminology, data standards, use of registries, and clinical trial networks capable of conducting future studies.

At the initial August meeting, Marjorie Jenkins, director of medical initiatives and scientific engagement at FDA's OWH, outlined the agency's initiatives in this area. Top NIH and NICHHD officials, plus representatives of the Centers for Disease Control and Prevention, the Agency for Healthcare Research & Quality, the National Vaccine Program Office, the Department of Defense, and the Department of Veterans Affairs also discussed previous and current research and ongoing challenges in obtaining needed information.

The next meeting is November 6-7, and additional sessions are scheduled for February and May 2018. A main topic for discussion is the ethical issues involved in including pregnant and lactating women in trials.

FDA initiatives

FDA's OWH has been examining these issues and funding relevant research projects for several years. A main task since 2015 has involved implementing a new regulation on providing more information for the pregnancy and lactation subsections of drug labeling. Areas of OWH research range from whether predictive modeling may help anticipate how pregnant women might respond to a drug without participating in a clinical trial, to the likely impact of Zika virus on pregnant women and their babies.

A leading OWH initiative is to encourage pregnant women to enroll in registries for certain drugs or diseases to help assess whether a therapy used to manage medical conditions such as asthma, diabetes, or high blood pressure raises special concerns. FDA can steer women and health professionals to more than 40 registries and additional resources on medication use during pregnancy, explained OWH deputy director Pamela Scott in a blog recently posted on the FDA website (view: http://bit.ly/2xhlixN).

The PRGLAC task force is slated to issue a report in two years that identifies federal research activities involving pregnancy and lactation, where further studies are needed to support the development of safe and effectives therapies for this population.

— Jill Wechsler

REGULATORY

EUROPE AND U.S. REGULATORS INCREASE COOPERATION ON INSPECTIONS

The European Commission, the FDA, and the European Medicines Agency (EMA) have signed a new confidentiality agreement that allows regulators on both sides of the Atlantic to share non-public and commercially confidential information, including trade secrets about inspections.

"This confidentiality commitment is a milestone in the ongoing implementation of the mutual recognition of inspections of medicine manufacturers and it aims to strengthen the EU-U.S. relationship," noted the EMA in a press release issued in late August. "Ultimately it will contribute to a more efficient use of inspection resources by regulators for the protection of human and animal health."

The EU and the U.S. have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific work, but complete exchange of information was not possible under these arrangements.

The new agreement formally recognizes that FDA's EU counterparts have the authority and demonstrated ability to protect the relevant information, according to the EMA statement.

"This step now allows the sharing of full inspection reports, allowing regulators to make decisions based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk," it concluded.

— Philip Ward

SUPPLY CHAIN

REPORT: CLINICAL TRIAL SUPPLIES MARKET WORTH $3.3 BILLION BY 2025

The global clinical trial supplies market is expected to reach $3.3 billion by 2025—at a compound annual growth rate of 7.3%, according to a new report by Grand View Research Inc. Driving factors for the growth include the rising volume of clinical trials, the increasing complexities in the conduct of these studies, and the spike in the number of biologics and biosimilar drugs entering clinical trials. Other impacting factors include geographic expansion and the development of IT in facilitating higher integration and smoother performance of activities.

Over the next eight years, the clinical trials and pharmaceutical industries are anticipated to continue steady growth, thereby promoting the high requirement of clinical trial supplies. In addition, with advances in supply chain management technology, the demand for efficient supplies are increasing. North America and Eastern Europe are expected to dominate the clinical trial supplies market over the forecast period, but the geographical distribution of clinical studies is slowly shifting from developed nations to regions such as Central and Eastern Europe, Asia Pacific, Latin America, and the Middle East.

Further key findings from the report suggest:

- On the basis of clinical phase, the market is anticipated to be dominated by Phase III trials in 2025. The presence of a large number of molecules estimated to reach Phase III by 2020 is the primary factor responsible for this prediction.
- Services in the areas of storage and distribution are anticipated to witness the fastest growth at a CAGR of over 7.0%.
- Key end-users in this industry are pharmaceuticals and biologics. Biologics are expected to experience the fastest growth, owing to the increasing research in the field of genetics and biotechnology, such as the development of nanoparticle-based drug delivery systems.
- In terms of therapeutic use or clinical indication, oncology dominates the market. A majority of cancer drugs require temperature sensitive distribution, which is further anticipated to fuel the growth of cold chain distribution.

The global clinical trial supplies market size was valued at $1.7 billion in 2016. The rising adoption of supply chain management systems is due to the growing pressure to cut down R&D costs and increase operational efficiency.

— Wire Report

CLINICAL TRIAL INSIGHTS

ENABLING HEALTHCARE PROVIDERS AS FACILITATORS OF PATIENT ENGAGEMENT

Recent study, and others in literature, inform misconceptions around physician and nurse involvement in clinical trials

Ken Getz

For more than two decades, the widely and frequently quoted statistic that only 3% to 5% of eligible patients participate in oncology clinical trials has served as unequivocal proof that the clinical research enterprise is failing to attract a reasonable level of patient participation. And the statistic has been a rallying cry for the cancer research community—and the broader clinical research community—to study and address the barriers to participation.

A number of factors that hinder patient participation have been discussed extensively in the literature, including: limited public and patient awareness and literacy; mixed patient attitudes and perceptions about clinical research; complex clinical trial designs with stringent eligibility criteria; inconsistent and poorly executed study recruitment strategies, planning, and tactics—particularly when competing with other actively enrolling clinical trials; and poor healthcare provider—both physician and nurse—familiarity with, and access to, clinical trials, combined with limited interest in referring patients.

A growing body of research calls to question the role of healthcare providers and suggests that this barrier is more nuanced and mischaracterized. Research suggests that healthcare providers possess a unique relationship with study volunteers that is untapped and holds the key to facilitating patient engagement. As clinical research and clinical care converge, healthcare providers will likely be the linchpin to engaging patients as clinical research partners.

A mission critical role

Healthcare providers play an essential role advising, guiding, and influencing patient participation in clinical research. Studies have consistently demonstrated during the past two decades that doctors and nurses are among the most trusted sources for health and medical information, including clinical trials. A recent CISCRP study found that the majority of patients (84%) state that they would consider participating in clinical trials if their physician recommended that they do so. And a high percentage (71%) of global study volunteers confirms that they spoke with their physician prior to making the decision to participate in a clinical trial.

Studies also indicate that patients who receive information about clinical trials from their healthcare provider are significantly more likely to participate. And patients who engage in frequent quality interactions with, and who receive an offer to enroll in a clinical trial from, their healthcare providers are also significantly more willing to participate.

To add to this body of knowledge, the Tufts Center for the Study of Drug Development (CSDD) recently conducted a study among physicians and nurses actively caring for patients across multiple disease conditions. Online surveys—one for nurses and one for physicians—were designed based on questionnaires from past scholarly assessments and on input from medical and clinical research professionals.

The surveys included questions about professional training, familiarity with and exposure to clinical trials; general attitudes and perceptions about clinical trials; comfort level and confidence referring patients into clinical trials; barriers to referring patients; clinical practice setting characteristics (e.g., type and size of practice and weekly patient volume); and background demographics.

The surveys were conducted in late 2015 and early 2016 and received 755 and 1,255 completed responses from physicians and nurses, respectively. Respondent race and ethnicity, gender, and disease specialty are representative of their respective populations.

Approximately half (48%) of physician respondents were female, with two-thirds Caucasian, 18% Asian, 10% Hispanic/Latino and 5% African American. The respondent sample was widely distributed across disease specialties. Top physician specialties included 35% internal/family medicine and 16% neurology and psychiatry.

Nurse respondents were predominantly female (85%) and Caucasian (82%) with wide distribution across disease areas of focus. Top disease specialties included cardiovascular (14%) and neurologic (10%) diseases. Only 2% reported focusing on oncology.

The majority of respondents (80%) from both surveys are based in North America and the remainder from Northern and Western Europe.

Familiarity and perceptions

Between 40% and 50% of physicians and nurses report being exposed to clinical research in medical and nursing school, and similar percentages have participated as clinical investigators or as research coordinators. A substantially smaller percentage—20% of physicians and 16% of nurses—have participated in clinical trials as study subjects/volunteers.

Nearly nine out of 10 physicians (88%) and seven out of 10 nurses (69%) report being "somewhat" and "very familiar" with the clinical trial process. Moreover, 86% of physicians and 69% of nurses, respectively, feel "somewhat" or "very comfortable" providing clinical trial information to their patients. An even higher percentage—91% of physicians and 72% of nurses—report that they feel "somewhat" or "very comfortable" discussing clinical trial opportunities with their patients.

Seven out of 10 physicians (71%) and nurses (69%) say they view clinical trials as a healthcare option for their patients. Forty-two percent of physicians and 43% of nurses indicate that their patients are inquiring about clinical trials more frequently than they did a few years ago.

Referral behavior

Physician and nurse interest in referring patients into clinical trials is very high, at 72% and 69%, respectively. However, the study found wide disparity in referral rates and referral volume between nurses and physicians. Six out of ten physicians reported referring at least one patient into a clinical trial during the past year. This is significantly higher than the 17% of nurses who reported doing so ($P<.005$).

Physicians report referring a median of five patients into clinical trials annually, a

CLINICAL TRIAL INSIGHTS

referral rate that is less than 0.2% of their annual clinical care patient volume. Nurse referral volume is considerably lower—a median of two patients annually—representing a .04% referral rate.

Eight out of 10 physicians (80%) and two-thirds of nurses (68%) indicate that they are most likely to refer their patients to colleagues with whom they are familiar and to well-respected and recognized regional or national opinion leaders.

Barriers to referral

Many academic studies—primarily focusing on oncology—have assessed the barriers preventing physicians and nurses from referring and enrolling their patients in clinical trials. The strongest barriers are time-based: lack of time to gather and evaluate clinical study information and insufficient time to discuss clinical trial information with patients. Physicians and nurses also cite the lack of sufficient information about clinical trials, overly stringent eligibility criteria, and the perceived burden for their patients to participate. The weakest barrier mentioned in all studies is the fear of losing patients to the principal investigator or another specialist.

In the Tufts CSDD study, looking across multiple disease specialties, several factors appear to increase the likelihood of physicians and nurses referring patients to clinical trials: distance between the clinical practice and the research center is inversely associated with patient referral rates; and physicians more involved in patient care are less likely to refer their patients.

Physicians who have never participated in a clinical trial as an investigator are significantly less likely to refer a patient (P<.0001). And more recent graduates from medical school are significantly less likely to refer their patients into clinical trials than are older colleagues (P<.0001). European physicians are 8.5 times more likely to refer their patients than their North American peers (P<.0001).

Nurses with a Master of Science in Nursing (MSN) degree and nurse practitioners were 8.8 times and 4.5 times more likely, respectively, to refer their patients than registered nurses (P<.001). Nurses in academic medical centers and in physician practices were significantly more likely to refer than those in hospital settings (P<.0001). European nurses were 14.3 times more likely to refer their patients than their North American counterparts (P<.0001).

Among both physician and nurse cohorts, gender, race, and ethnicity were not significant predictors of referral behavior.

> The widely accepted and cited statistic on low patient participation rates overgeneralizes and mischaracterizes the enrollment challenge.

Necessity and opportunity

The results of the Tufts CSDD study are very consistent with those published in the literature, with some additional insights. Nearly half of healthcare providers have been exposed to clinical research training during medical and nursing school. The majority of physicians and nurses are interested in referring their patients into appropriate clinical trials; self-report feeling familiar with the clinical trial process and feeling comfortable providing clinical trial information to, and discussing clinical trial opportunities with, their patients.

The study findings indicate that a high proportion of physicians actively referred their patients into clinical trials during the past year but the reported referral volume is very low. Indeed, the referral volume is well below that dictated by clinical trial eligibility criteria alone. Low referral rates contrasted against a high comfort level and willingness to refer suggest that healthcare provider referral behaviors are more nuanced and complicated.

Most physicians and nurses want to actively advocate for their patients and provide access to the best healthcare options available—including investigational treatments in clinical trials. Having established more intimate relationships with their patients, physicians and nurses facilitate enrollment in specific clinical trials based on their subjective assessment of each patient's unique ability and predisposition to enroll and participate.

The Tufts CSDD study findings suggest that healthcare providers rely on the strength of their personal knowledge and their mental and physical closeness to clinical research: who is conducting the clinical trial, and where it will be performed (i.e., convenient proximity and reputation of the research center). The reasons why physicians and nurses choose not to refer patients are addressable and largely associated with the need for more information that can be conveniently and quickly reviewed and processed. Creative, compelling, easily accessible, and integrated medical and professional education programs will help address this need. Dedicated, rich-content interactive channels and communities may be important conduits. Well trained, roving clinical research education liaisons within healthcare settings may also prove effective.

The widely accepted and cited statistic on low patient participation rates overgeneralizes and mischaracterizes the enrollment challenge. The recent Tufts CSDD study—along with those in the literature—refutes long-held notions that healthcare providers are insulated from, and disinterested, in clinical research and resistant to referring their patients into clinical trials. The study results also indicate that healthcare providers are better positioned than expected as patient engagement facilitators if they have sufficient time, information, and confidence to advocate on behalf of their patients.

— 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

CLINICAL TRIAL MANAGEMENT

OVERCOMING COMPLEXITIES OF CLINICAL TRIAL SUPPLIES IN LATIN AMERICA

Supply chain strategies require a close look at the regulatory factors and the drug import hurdles and hopes in the region

Juan Bamberger and Roopal Patel

Latin America is a dynamic region that shares similarities in cultures and social development. However, there is a wide diversity in government policies; hence, there is no unified and consistent way of handling foreign trade operations.

Latin America has continued to stay attractive for clinical research because of the amplitude and diversity of the regional population. The conduct of clinical research in Latin America has matured over the last few decades, requiring government authorities to develop and/or clarify new regulations in the areas of trade compliance.

To develop a well-defined strategy for importation processes and ensure a continuous supply chain for clinical trials, it is imperative to be able to answer two questions: How does this regulatory evolution impact the import process, and what are the main import challenges and opportunities faced in Latin America?

Parties in the importation process

Moving products across borders may sound simple, but it is important to understand the roles of all parties involved to learn and understand the complexity throughout the process.

CROs. General practice in the pharmaceutical industry is to delegate the conduct of a clinical trial to a contract research organization (CRO). This article will concentrate on import activities related to clinical trials and products such as investigational medicinal products (IMPs), non-IMPs, medical devices, and ancillaries.

Importer of record (IoR). The IoR is the party responsible for compliance with trade regulations of the importing country whose legal entity and associated tax numbers are used for import activities. As the importer, the party has three main legal responsibilities: ensuring the imported goods comply with local laws and regulation (including the end use of the products), filing an accurate and complete customs duty entry and presenting associated documents, and paying the assessed import duties and other taxes on those goods.

Interface between CRO and IoR. The CRO's responsibilities could include managing the import and export activities for the clinical trials. The study sponsor may or may not contract the IoR services to the CRO; therefore, the sponsor could also act as the IoR in the selected countries. Which party can act as the IoR is dependent on the regulatory and legal framework of the country. It is important to have a clear and thorough discussion of this topic during contracting and project setup.

Customs brokers. A customs broker is a person or a party who is licensed by the local customs authority to perform formalities for shipments on behalf of the importer or the exporter. They are responsible for preparing and submitting documents required for customs clearance, paying import duties and value-added tax (VAT) at customs, and/or submitting shipping documents to other government agencies.

Ministry of Health (MoH). The MoH is the governmental ministry or agency responsible for the regulations and approvals of pharmaceutical products, sanitary standards, regulations of the food industry, and import and export licenses. The authorities of the various countries are listed in the map.

Customs. Customs is a state public office, located at the borders, airports, and/or seaports, where the goods that are imported or exported are registered, and the duties are assessed according to the corresponding tariff. Customs, in basic terms, function as the first filter for international shipping, mitigating any risk for the countries. Customs authorities are in charge of ensuring that all the goods entering the country are compliant with regulations, secured, and properly classified for taxes.

Developing processes to meet customs requirements is the first challenge for imports related to the conduct of clinical trials.

Latin American countries

Latin American countries such as Argentina, Brazil, Chile, Colombia, Mexico, Peru, Costa Rica, Ecuador, Guatemala, and Panama vary politically and economically, leading to highly complex restrictions on goods for importation. In contrast, some of the countries have streamlined processes simplifying the import process for companies.

The import process of medicinal products often requires import licenses. The import requirements for other clinical trial materials are dependent on the Harmonized Tariff Code, the end use of the product, and the country's government agency's regulations for the product.

Countries with high complexity

Argentina. Argentina is considered one of the most complex countries for performing importations for clinical trial supplies. Many items such as printed documents, measuring devices (rulers, stadiometer, etc.) and electrical products (laptops) are governed by various agencies and require specific certifications. Hence, it is critical that all items that will be imported are identified in advance prior to submitting the protocol to ANMAT (the MoH in Argentina).

CLINICAL TRIAL MANAGEMENT

With all the items being identified, a complete review of the import requirements can take place with the CRO's Global Trade Compliance team. Then collaboratively, it can be determined if the items should be imported or purchased locally. Purchasing locally can result in cost savings and avoidance of complex import requirements.

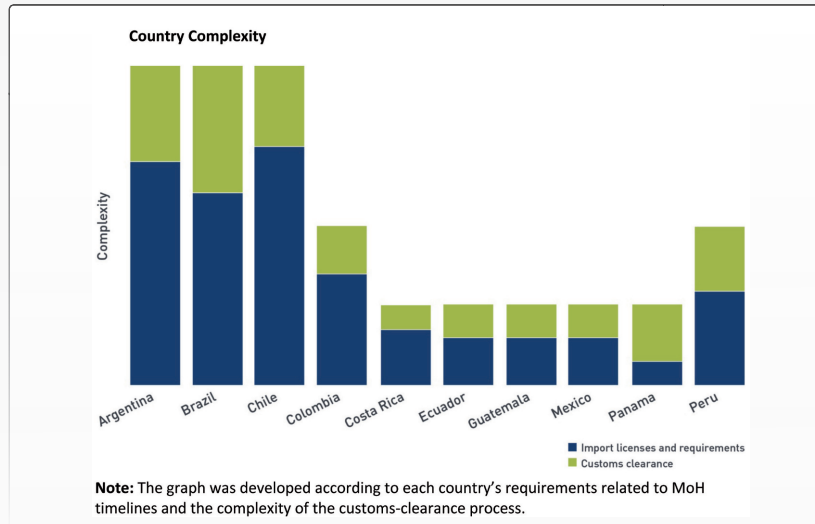
Brazil. In Brazil, the MoH (ANVISA) requirements and timelines for importation have improved; however, the need for obtaining numerous import approvals has remained.

Depending on the clinical supplies and the regulatory approval strategies, one of three types of MoH import regulations can be used:

- RDC 39/2008 requires a general license with the total quantities of all supplies to be applied for and approved by the MoH prior to shipment.
- In RDC 09/2015, an umbrella general license is not required and the importer is able to import any quantity needed for conducting the clinical trial. However, the import license is applied for approval just prior to the cargo arriving in Brazil, and the regulation is only applicable to medicinal products.
- RDC 10/2015 follows the same procedures as RDC 09/2015, but it is applicable for medical devices only.

Furthermore, the timelines for the MoH import license approval are high and change from time to time depending on the MoH workload. The MoH can take from seven to 45 days to approve and release an import license at Guarulhos Airport in the state of São Paulo. If a shipment requires an import license prior to shipment, the timelines can increase to 55 days.

Currently, due to their high workload, the MoH at Guarulhos Airport is receiving support from the MoH of other states of Brazil. Most CROs and pharmaceutical companies are based in São Paulo and the Guarulhos Airport is requested since they have experienced staff for processing shipments for clinical trials. Thus, the MoH headquarters are working to decrease the import licenses timelines to seven days by the end of 2017.



Note: The graph was developed according to each country's requirements related to MoH timelines and the complexity of the customs-clearance process.

Peru. The import process in Peru is challenging when it comes to customs clearance. Customs in Peru are very stringent and demand that all the information in the shipping documentation match perfectly with the content of the import license, which may significantly delay the customs clearance process if there are any discrepancies.

Separate import licenses are required for drug and ancillary supplies, which are subjected to MoH availability to be approved, meaning that submitting both import licenses at the same time does not mean they will be approved on the same day. This is very important to keep in mind in studies in Peru.

Chile. Chile's restrictions to import IMPs have increased in complexity in the last two years. Both customs and MoH (known as ISP in Chile) have started to closely collaborate to ensure compliance of all regulations related to the import of medicinal products. It is required to submit an import license per shipment to the MoH, and the MoH does not allow the distribution of the medicinal product if the information in the shipping documentation, import license, and study protocol do not match.

It is critical that lot numbers of medicinal products, expiry dates, and corresponding certificates are accurate and provided to the MoH; otherwise, the import license that will allow distribution of the medicinal products to sites will not be granted.

Fortunately, imports of the majority of medical equipment do not require any import license. There are some exceptions, such as importing hypodermic needles, which require a specific import license, and the process is complicated. Similar to Argentina, it is recommended to outline the entire list of supplies that are used in the clinical trial and collaboration to be set up with the CRO's Global Trade Compliance team to outline any obstacles and opportunities.

Countries with medium complexity

Mexico. Mexico, being the only Latin American country located in the northern part of America, yet being connected to rest of Latin America, offers logistical advantages to the pharmaceutical industry for conducting clinical trials. The MoH is involved in importation approval; however, Mexico has developed a unified system for import and an export license submission, which is linked between the MoH and customs, allowing shortening of timelines from the submission to the approval.

Mexico also offers special benefits of reduced import tax for imports related to clinical research. Additionally, there are ad-

vantages of free trade agreements between Mexico and other countries, where only MoH approvals for studies are required and there are limited import license requirements.

Colombia. In order to import drugs for clinical investigation, the medication must be approved by INVIMA (the MoH in Columbia) as a general import license; afterwards, an import license per six months or per shipment must be applied for.

Colombia is an attractive country to conduct clinical trials; however, medical equipment must be verified in advance because depending on the product to be imported, different certifications from different government agencies might be applicable and formal clearance through a customs broker is mandatory.

Countries with low complexity

Costa Rica, Ecuador, Guatemala, and Panama are constantly working on putting their names on the map of conducting clinical trials. Hence, there are limited import requirements for ancillaries and medical devices, and they follow the general process of trade facilitation commonly used by many countries.

Other considerations

Latin America has different particularities to consider for clinical trials. Therefore, it's necessary to review the following topics that are related to the import processes and their implications.

MoH approval timelines and requirements. As soon as a new protocol is approved by the MoH, the import process can start. It is important to consider the timelines for clinical trial application (CTA) or import licenses approvals by the MoH. The approval timelines range from two to six months depending on the country.

Import barriers and risks. Latin American local authorities still consider shipments for clinical trials as commercial shipments (for sale) and often apply commercial requirements to the shipments, requiring documents that are not available for clinical supplies. Furthermore, communication between customs and other government agencies is limited, leading to confusion about the purpose of the supplies and delayed shipment clearance.

Looking forward in the region

Latin America has started to harmonize some of the importation processes and started to leverage technology to facilitate trade.

Online procedures/licenses. Countries have started to move from manual processes to electronic systems in order to improve the communication between authorities and better control of shipment documentation.

- **Argentina:** MoH has a project to implement a new electronic portal which will allow the submission of new clinical trial protocols via a website, reducing the approval timelines.
- **Chile:** Implemented "GICONA—Gestión de Información del Instituto de Salud Pública de Chile": This is the online MoH platform to submit import license, CTA, extensions, and amendments.
- **Colombia:** An online platform "VUCE—Ventanilla Única de Comercio Exterior" was implemented to submit import licenses.
- **Mexico:** "Ventanilla Única": Customs system that allows customs authorities to maintain a fiscal database, including all importers, and simplifying the custom clearance process.
- **Peru:** Online import license submission is possible via the "VUCE" platform.

Dynamic region, specialized staff, and adaptation skills

Since the pharmaceutical industry has identified Latin America as a viable option for clinical research, not only have the regulations evolved, but the number of technical and specialized experts has increased to meet the industry's needs to provide adequate and trained professionals for clinical trials development.

In Brazil, the CROs Association (ABRACRO) plays a very important role to contribute to the development of clinical research, collaborate to improve regulatory processes, and promote scientific and educational actions related to the activity in the country. ABRACRO has collaborated to create the first graduate program in clinical research in São Paulo, aiming to reduce the gap in the training of professionals in the segment and also stimulate the improvement of those who already work in the specialty. This association also provides workshops and forums.

Additionally, there is an import and logistics committee at ABRACRO, which meets to align import processes and share experiences. A customs broker with high expertise in clearing all CROs' cargos is present. The broker brings regular issues, queries, and new trends with MoH and customs to the table. As a result, the CROs' customs clearances are having standard processes.

With specialized public education, Mexico's largest universities (UNAM and IPN) offer bachelor degrees in foreign trade and international commerce at no cost.

In Argentina, there are five top universities from Buenos Aires that offer bachelor degrees in international trade. All of them are private and their programs last four years on average.

Furthermore, the most important university at a national level (UBA) offers a postgraduate degree on business management of foreign trade and integration.

Conclusion

Importation for clinical trials in Latin America can become highly complex and increase study timelines. Therefore, prior to initiating a new clinical trial, a detailed analysis of all the supplies that will be imported needs to take place. By collaborating with the CRO's Global Trade Compliance team, an import and export strategy can be developed to reduce timelines, decrease cost, and leverage trade provisions to optimize the supply chain.

— Juan Bamberger is Manager, Global Trade Compliance; Roopal Patel is Senior Director & Global Head, Global Trade Compliance; both with PAREXEL International

NEWS NOTES

REPORT SHOWCASES ROLE OF PENNSYLVANIA LIFE SCIENCES INDUSTRY

A newly released study shows that Pennsylvania's life sciences industry has been advancing at a steady rate and generated more than $88.5 billion in total value to the state in 2016. Through increased federal funding, patent applications, and entrepreneurship, Pennsylvania maintains a lead over much of the rest of the country in terms of R&D, according to the independent report produced by KPMG.

The report also found that the life sciences industry in PA directly employed 112,000 people during 2016 and was responsible indirectly for an additional 230,000 jobs through business purchases and household expenditures. PA had the highest 2016 National Science Foundation (NSF) funding rate in comparison to peer states and was awarded the second highest NSF and NIH funding per capita.

MedSource adds new service line

Houston-based CRO MedSource is growing its service-offering to include the early stages of clinical development and pipeline planning through investigational new drug (IND) submissions. The service will be provided by a new department within MedSource—Scientific Development. In addition to entering the early-stage space, MedSource is opening a new office in the Cambridge Innovation Center in Cambridge, MA.

ProQR spins out CNS-focused company

Netherlands-based ProQR Therapeutics N.V. has spun out Amylon Therapeutics, a privately-held company focused on the development of therapies for CNS disorders, with seed funding from a group of institutional and private investors. As part of the transaction, ProQR has granted an exclusive license to Amylon to develop therapeutics for beta amyloid-related disorders.

Lyndra and Allergan ink pact

Boston-based startup Lyndra Inc. has struck a partnership with Allergan to develop orally administered ultra-long acting products for the treatment of Alzheimer's disease. The basis of the collaboration is Lyndra's innovative sustained-release technology, which has the potential to transform drugs typically dosed daily to once-weekly oral dosing.

Novartis launches mobile MS study

Novartis has launched the first large-scale mobile research study for people with multiple sclerosis that collects data via their smartphone, without the need for clinic visits. The study, called Evaluation of Evidence from Smart Phone Sensors and Patient-Reported Outcomes in Participants with Multiple Sclerosis (elevateMS), is designed to collect sensor-based data from physical tasks and symptoms.

— Staff and wire reports

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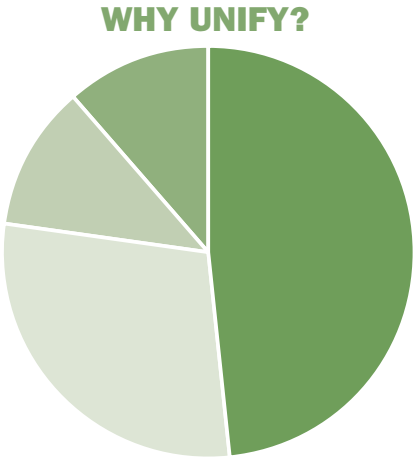
Benefits of R&D Collaboration

Learn to partner effectively in the era of collaboration, where the benefits gained will outweigh the challenges if approached correctly



Note: Other responses include novel science, third-party validation of products through the research, and greater level of patient care/access.

COLLABORATIVE R&D

Collaborations in clinical trials, or the clinical research enterprise as a whole, are not new. But in a recent survey with our partner SCORR Marketing, we found those collaborations are—and will continue to increase.

In our survey, we delved into areas such as which types of collaborations are more pervasive and those that are increasing; the benefits of collaborations, as noted in the chart; and the challenges, which included loss of control over project management, incompatible company cultures, legal or IP issues, lower than expected time, and cost savings.

In response to our question, "the rise in which of the following is the primary reason for the upward trend in collaborative R&D arrangements," the second and third answers were technology-related—big data at 27% and cloud technology at 13.5%. Clearly, technology is the backdrop by which all stakeholders in this survey—academia, biotech, contract research organizations (CROs), sponsors, research sites, and service providers can facilitate greater collaboration.

In this section, we present information on technology's role in collaboration, from Jim Streeter, vIce president of life sciences for Oracle, and strategy and management consultant Candice Hughes shares her views on the keys to improving and de-risking alliances and partnerships.

— Lisa Henderson

Please download the free report at http://bit.ly/2wfONjX

A Catalyst for Safer, More Efficient Trials

The emergence of cloud-based eClinical software is setting pharmaceuticals in good stead for significant progress. Cloud-based systems are well placed to unify disparate systems and enable pharmaceuticals to integrate each component of their drug development cycle into a distinct central database. This will help eliminate duplicate processes and allow different departments to work off a single and complete view of the data. This, in turn, can speed up the analytical processes of clinical trials, so that drugs can be brought to market faster.

In addition, the better visibility of data that cloud-based software provides can speed up and enhance decision-making. For example, teams can more quickly prepare submissions for biostatistical analysis and share the lessons learned with the organization for future improvements. Take QuintilesIMS, the world's largest CRO. The company offers its customers a real-time view of clinical trial data so it can evaluate progress and quickly adjust practices if needed.

Cloud-based systems also provide efficiencies from a regulatory standpoint. With a clear view of where

ALLIANCE EXAMPLES

#1
INDUSTRY—INDUSTRY

PROJECT DATA SPHERE—GLOBAL ONCOLOGY BIG DATA ALLIANCE. The Global Oncology Big Data Alliance (GOBDA) is a recently announced joint alliance, co-led by Merck KGaA, Darmstadt, Germany, and Project Data Sphere, an independent, not-for-profit initiative of the CEO Roundtable on Cancer's Life Sciences Consortium. GOBDA was formed to expand the open-access of de-identified patient data sets to further enhance analytical capabilities specifically for rare tumor patient data. The joint alliance builds on Project Data Sphere's current platform, which contains historical clinical trial data from almost 100,000 patients provided by multiple organizations. Leveraging these data on the platform with big data analytics will help to optimize clinical trials, build a registry of data, and help to enable advancement in the understanding of cancer treatment globally. In addition, by unleashing analytical power and big data to study and learn how to better manage rare but serious immune-mediated adverse events, institutes and industry will be able to assist regulators to adapt these new learnings into treatment guidelines, as well as establishing models to help enable early adverse event identification and improved patient outcomes. "The ultimate goal of our alliance with Project Data Sphere is to unleash the power of big data to bring value to cancer patients," said Belén Garijo, member of the Executive Board of Merck KGaA, Darmstadt, Germany, and CEO of its healthcare business. The anticipated overall term of the GOBDA project and strategic collaboration will be from 2018-2021.

#2
ACADEMIA—INDUSTRY—SERVICE PROVIDER

BEAT AML MASTER TRIAL. Announced in October 2016 by the Leukemia & Lymphoma Society (LLS), the Beat AML Master Trial is a collaborative clinical trial for acute myeloid leukemia (AML). With guidance from the FDA, and LLS as the sponsor, the trial uses a precision medicine protocol that employs comprehensive genomic profiling to find and match specific AML genetic mutations in newly diagnosed patients over age 60, with an investigational drug or drug combination best suited to attack the specific molecular mutations causing the cancer. The trial started in February and LLS anticipates that 500 patients will be enrolled, with the study lasting from one to three years. As of July, six leading cancer centers have enrolled more than 70 patients, and four more institutions are expected to join the study this year. Four sponsors—Alexion, Boehringer Ingelheim, Celgene, and Gilead Sciences—are participating by offering investigational drugs, none of which are yet approved. At least three more pharma companies are expected to join the trial. Other collaborators include: Foundation Medicine, which utilizes its proprietary genomic profiling assay for hematologic malignancies, for all of the patients; INC Research manages the logistics of the trial; Protocol First provides a web-based digital application to guide the clinicians; myClin provides a communications platform between the clinical trial sites for engagement and regulatory compliance; and Medidata's Clinical Cloud solution will be used for data capture, management and reporting, and medical coding.

#3
ACADEMIA—GOVERNMENT

I-SPY 2 CLINICAL TRIAL. I-SPY 2 is a partnership and collaboration between QuantumLeap Healthcare Collaborative (QLHC), Foundation for the National Institutes of Health, FDA, National Cancer Institute (NCI), 16 leading academic centers (researchers and physicians), the Safeway Foundation, and patient advocates. It is a standing Phase II randomized, controlled, multicenter study with an adaptive design aimed to rapidly screen and identify promising new treatments in specific subgroups of women with newly-diagnosed, locally-advanced breast cancer (Stage II/III)—regardless of sponsors company. The innovative design utilizes biomarkers from each woman to assign her to a particular investigational drug. The trial learns as it goes, as each patient's response to a particular drug informs how the next patient will be assigned to a treatment arm. Drugs with a strong efficacy threshold for a particular patient group may "graduate" to a more focused Phase III drug registration trial, while drugs found to be ineffective or with significant side effects are quickly dropped from the trial. I-SPY 2 graduate neratinib, from Puma Biotechnology, was approved by the FDA on July 17, as NERLYNX for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. QuantumLeap was established in 2005 as a collaboration between medical researchers at University of California, San Francisco and Silicon Valley entrepreneurs to accelerate the transfer of high-impact research in clinical processes and systems technology into widespread adoption.

SHUTTEROK/SHUTTERSTOCK.COM

data is stored and how it runs between teams, organizations can process compliance reports or respond to health authority requests faster.

Identifying new correlations

Along with bringing efficiency to the drug development lifecycle, a more unified approach to data will enable scientists to discover new relationships in their data sets that could stimulate the creation of potentially life-saving therapies.

One pharmaceutical company worked with PwC to uncover why a promising cancer treatment was failing in certain Phase III trials and to identify more appropriate candidates for future studies. Analyzing clinical and biomarker data from Phase II and Phase III trials helped attribute the therapy's failures to a genetic imbalance in some patients suffering from the rapidly developing disease. As a result, the company was able to pinpoint several valuable biomarkers to help determine which patient groups to target and exclude in future trials.

Opportunities with machine learning

Collating, analyzing, and processing the entirety of a company's data in a centralized way will also lay the groundwork for the success of technologies such as machine learning and artificial intelligence (AI), which will further enhance analysis.

Although AI technology is still in its initial stages, we will see it being applied increasingly to help drive efficiency within pharmaceutical businesses. For instance, intelligent algorithms could automatically modify manufacturing capabilities to avoid product shortages by forecasting future supply and demand for new drugs.

AI also paves the way for more accurate candidate selection for clinical trials, working to reduce patient safety concerns. Analyzing data from the thousands of trials conducted will expose warning signals for potential safety risks. And as this data set expands, the level of insight it reveals will rise, and the probability of selecting at-risk candidates will decrease. Pharmaceutical companies are under a great deal of pressure to develop drugs faster while ensuring the highest levels of patient safety, and advances of this kind will be key to achieving this.

However, it will take more than technology to speed up clinical trials. To make the most of eClinical platforms, a cultural shift is also needed.

Research scientists have become accustomed to working in isolation for years, both due to the structure of their organizations and the limited technologies they work with.

The transition to fully cloud-based eClinical platforms will require different approaches to working as well as more collaboration between teams throughout the drug development process. And with a collaborative culture, unified practices and a roadmap in place, pharmaceutical organizations will be well placed to accelerate and advance the nature of drug development in a significant, life-saving way.

— Jim Streeter, Vice President of Life Sciences, Oracle

Good Partnering Yields Value

A good example of the value of partnering is Novartis's recently approved CAR-T therapy that was developed in collaboration with the University of Pennsylvania. With these and other successes, alliances are a necessity in the current market because the high cost of innovation means firms want to spread the risk through partnering. Besides risk, innovation requires an entrepreneurial culture that is far easier to grow and foster at an agile, smaller firm than it is at a large, global firm that may be risk adverse and focused on cost-cutting.

Partnering also is crucial for clinical trial operations involving outsourcing to universities, research hospitals, and CROs. While operating costs may be lowered, risks can potentially be increased, leading to costly regulatory and legal fines if partners are not carefully chosen and managed.

While collaboration for innovation or cost-saving can be effective, there are a number of challenges that need to be overcome to ensure a partnership or alliance will be effective. In fact, these challenges are so strong that 60% of overall business strategic alliances fail, according to a recent CMO Council report. Failing partnerships cause employee stress and burnout. Great managers recognize the double-edged sword of alliances that are both critical to success and a danger with the potential for serious harm. The result of not assessing soft factors and choosing a poor partner negatively impacts firms in three critical areas: delayed or lost revenue, financial losses due to fines or lawsuits, and reputational damage.

The one reason alliances fail

The key reason that alliances and partnerships fail is insufficient investigation and assessment of soft factors prior to and throughout the relationship. Soft factors include: corporate culture, alignment of goals, compatibility of alliance staff, similarity of processes or modification to suit the alliance, and clear and consistent communication, especially relating to goals and responsibilities.

Along with these soft or human factors, partners need to perform strategic analysis to predict the most likely future situations that could impact the alliance, including goals and human factors. For example, while the partner's goals seem to be aligned at the start of the alliance, what does each partner marketplace look like in three years? In five years? Will the goals be likely to remain aligned? Will staff turnover be elevated due to marketplace or other changes?

While partners are used to and commonly check hard factors such as financials, technological specifications, cost-sharing, legal term agreement, and so forth, there is rarely an established process for checking soft factors, which are inherently difficult to assess.

Create a risk-based plan for assessment

On the positive side, pharmaceutical firms are well used to assessing and mitigating risk. It's what they do day in and day out in their highly skilled regulatory departments or via other partners with expertise in this area. They or their partners can assess the risk failure overall or in specific areas respective to the firm. Once the areas of greatest

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Senior Medical Director, QuintilesIMS

Gavin Nichols
VP CRO/Life Science, Perspectum Diagnostics

Moderator:

Lisa Henderson
Editorial Director, *Applied Clinical Trials*

The race is on to find a treatment for Nonalcoholic Steatohepatitis (NASH), a silent liver epidemic that's asymptomatic and hard to diagnose. A next-generation approach to NASH clinical trials uses anonymized EHR and claims data, non-invasive diagnostics, and innovative site models. This can help you speed recruitment, optimize sites, shorten timelines and cut development costs.

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For technical questions about this webinar, please contact Kristen Moore at kristen.moore@ubm.com

De-risking Alliances/Partnerships for Less Stress, More Success

What you see...	What to do now...	How to vet next partner/alliance
Flood of urgent emails	All hands team meeting to listen	Interview/survey for cultural & personnel fit
Partner/alliance firm silence or complaints	1. Conduct senior lead meeting to re-establish goal & process alignment 2. Overhaul communications for clarity & concreteness 3. Establish check-ins 4. Initiate partner/alliance goal & market analysis now, 3 year, 5 year	1. Interview & assess current goal alignment 2. Market analysis partner/alliance firm, future predictions of goal change (3 year, 5 year)
Sudden meeting request from manager	Provide all-hand meeting feedback, changes made, goal alignment analysis	Report on fit and goal alignment assessment with go/no go decision

Source: Hughes BioPharma Advisers

Strategies in de-risking partnerships and alliances involving three scenarios.

risk with the partner have been identified, the firm can initiate a plan to perform de-risking due diligence.

Culture, for example, can be assessed via in-person observation, interviews, and surveys combined with analysis of online and media communications. A firm can conduct these types of analyses on its own. However, the company needs to be alert to bias and unintentional misdirection. First, it is hard to assess one's own culture for the same reason that it is difficult to proofread something one's written—it is hard to look clearly and carefully with no emotional or other bias at one's self. A firm's stated culture may differ from the day-to-day situation. Secondly, when people know they are being observed, especially by a potential partner, it is hard to avoid acting on one's best behavior. Thus, the results should be weighted to reduce bias or misdirection or the assessments can be performed by an outsider.

True short- and long-term goals can be determined by gathering the data through several approaches and assessed by comparing them to the most logical and probable goals for the situation. First, discuss goals with your potential partner. Those are the stated goals. Then examine goals provided via the media or other public information. From market research, competitor analysis, industry projections, and other data, probable and likely future goals can be determined. How do the goals match up? Even if they are not aligned, there could be a variety of reasons why. What is important is to assess how stated and projected goals match your firm's goals. If there is misalignment, why, how much. and should further action be taken?

Key start steps

Communication is as critical as goal alignment and culture. Do the partnership teams have solid communication plans in place that have been agreed to by both sides? If not, this should be the first step for the new partnership. Along with the plans, should be clear responsibilities that don't overlap. Additionally, procedures for frequent and regular status check-ins, along with milestones, should be defined at the beginning. The status discussions should not be rote, verbal "okay" confirmations, but should include checklists or completed work and next steps with appropriate confirmation of completed work. Partners could have differing views on completed work.

If the initial procedure setup does not go well, that is a clear sign that something was missed during the soft-factor due diligence and that should be revisited to determine where the partnership is going off course and how it can be resolved to get back on-course.

When the due diligence process finds a problem area, the partners need to find a way to compromise or work around the challenge point. For example, if assigned personnel have strong incompatibilities, consider assigning a new team member. Even if they are less skilled functionally but a better fit personally, they may be able to work under or with the person with superior functional skills to gain that knowledge while enjoying a more harmonious partner team.

Symptoms that a partnership is struggling include a sudden uptick in urgent emails, silence or complaints from the partner firm, and abrupt complaints to management that trickle down to the personnel on the partnership team (see chart). Many of these issues relate to poor communication during the partnership, goals becoming misaligned over time, or inadequate initial due diligence. Getting to the true cause of the problem means there is a good chance of resolving it. A number of common situations and resolutions are included in the chart.

> The key reason that alliances and partnerships fail is insufficient investigation and assessment of soft factors prior to and throughout the relationship.

Appropriately de-risking the partnership up front, even given added costs, is the right approach to avoid much worse costs six months, a year, or a few years down the road. It is easy to want a partnership and overlook challenges or to want costs lowered right now and overlook more distant costs. Easy wins can be false wins. Success often comes from taking the harder path.

— Candice M. Hughes, PhD, MBA, strategy and management consultant, Hughes BioPharma Advisers

Mitigating Supply Chain Risk in Clinical Trials

Chad Presher, Adam Sheriff, Lorna Briddick

Outlining a decision-making framework that integrates real-world signals with supply planning techniques to reduce risk and avoid potential interruptions.

PEER REVIEW

A *Business Insider* article from March 2015 explores the impact Queen Elizabeth's passing will have on Great Britain.[1] The author states that "The death of Queen Elizabeth will be the most disruptive event in Britain in the last 70 years." The article goes on to detail exactly what will happen to the country as it works to recover from this uniformly tragic event. For example, the author states that "For at least 12 days…Britain will grind to a halt." and "Whatever happens formally…Britain effectively ceases to function." Additionally, the article points out that the British Monarch is the official head of state for several other countries, including Canada, Australia, and New Zealand. It is not unreasonable to anticipate that the Queen's demise will also have a meaningful impact in these countries.

For the pharmaceutical industry, a significant amount of drugs supporting clinical studies flow through the U.K., both directly to clinical sites in the U.K. and for onward distribution to other countries (see Figure 1 on page 30). Should there be a halt to normal business operation in the U.K., the impact to clinical trials could be significant, leading to supply interruptions to potentially life-altering clinical therapies. Additionally, because the patients this industry serve are at the core of everything it does, ensuring the supply of clinical drugs during a time of crisis is a necessary moral and ethical action to take.

To that end, the clinical drug supply team at Biogen, in conjunction with Brizzey, a clinical supply chain management company, developed a decision-making framework that integrates real-world signals with supply planning techniques to proactively reduce supply chain risk and avoid potential supply interruptions.

Project origin

In April 2010, the Eyjafjallajökull volcano erupted in Iceland. The resulting ash cloud wreaked havoc in Europe, resulting in significant and unprecedented interruptions to all modes of transportation. Air traffic was halted over much of the continent. The capacity of the road and rail transportation network was overloaded. At the same time, French rail workers went on strike. In the aftermath of the eruption and with the added challenge of the French strike, moving anything into or out of Europe became enormously challenging. The pace of commerce slowed and, in many cases, supply chains came to a standstill.

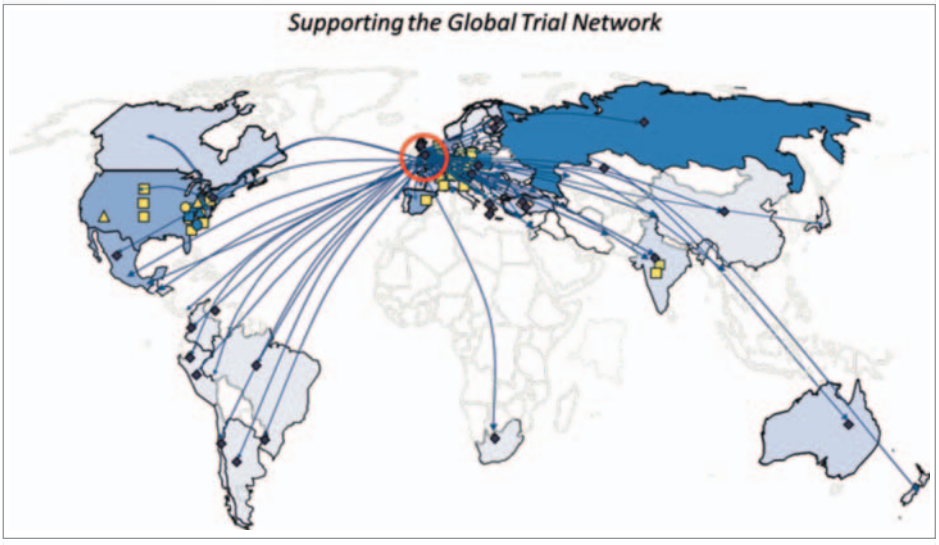
Although the 2010 eruption of Eyjafjallajökull resulted in a very challenging period for clinical supply managers, it did present a valuable learning opportunity. Four years later, in late August 2014, the tectonic plates under Iceland were shifting again: earthquakes were being observed in Iceland and, this time, the Bardarbunga volcano was threatening to erupt. Having narrowly avoided supply interruptions due to the Eyjafjallajökull volcano eruption, our team chose to react very differently in 2014 than it did in 2010.

As soon as news broke that the Bardarbunga volcano could erupt, our leadership team put into action a proactive response. First, working with the appropriate contract research organization (CRO) partners, the team contacted the clinical trial sites to understand their in-clinic inventory positions. Then, based on the site inventory levels and the assessed potential supply interruption risk, manual shipments were raised to get all European site inventories back up to maximum levels. Additionally, the supply managers worked closely with the quality and distribution partners to prioritize any shipments going into or out of the U.K. distribution centers. In parallel, the team identified alternate

shipping routes (e.g., directly from the U.S. to Japan instead of to Japan via the U.K.) and contacted vendors to understand courier contingency plans and options. Ultimately, the Bardarbunga volcano did not erupt. However, our clinical drug supply team learned a lot from the exercise and decided to create a project to turn this one-off action into a robust methodology.

At the core of this project is a desire to maximize the action period before potential supply interruptions. The goal of this methodology is to proactively respond to the signals that may precede significant events with the potential to cause supply disruptions. The team believes that, by monitoring real-world information, precursor signals can be identified. Some examples of this principle are: An earthquake in Iceland may predict a volcano; rioting may lead to significant geopolitical unrest; the Queen of England being admitted to hospital may signal that her passing is near (see Figure 2).

Central Supply Hub



Source: Presher et al.

Figure 1. A large amount of drugs for clinical studies flow through the U.K., supplied for its own sites and distributed to several other countries globally.

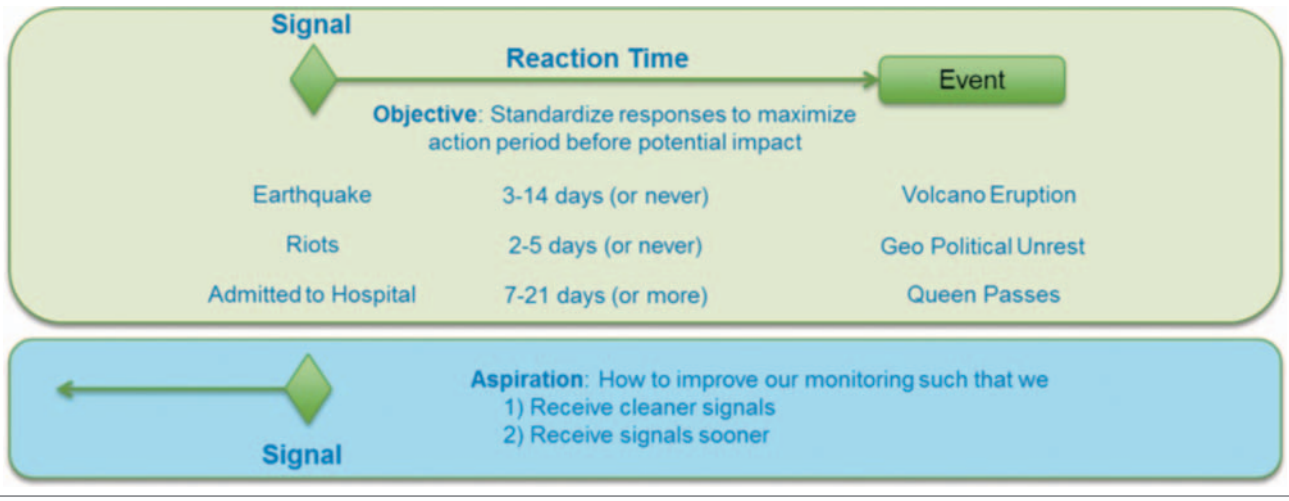
A five-step approach was taken to create this methodology:

- The team explored the practice of failure modes and effect analysis (FMEA).
- Both a proactive and reactive response process was defined.
- Key tools and teams needed to support this process were identified.
- Connections to existing Biogen tools and teams were developed.
- Finally, the necessary tools and templates than connected all of these business processes together were built.

Failure modes and effects analysis

The first step of this project was to explore common risks to clinical supply chains through the use of FMEA, a systematic tool for evaluating potential risks to a product or project. The team brainstormed

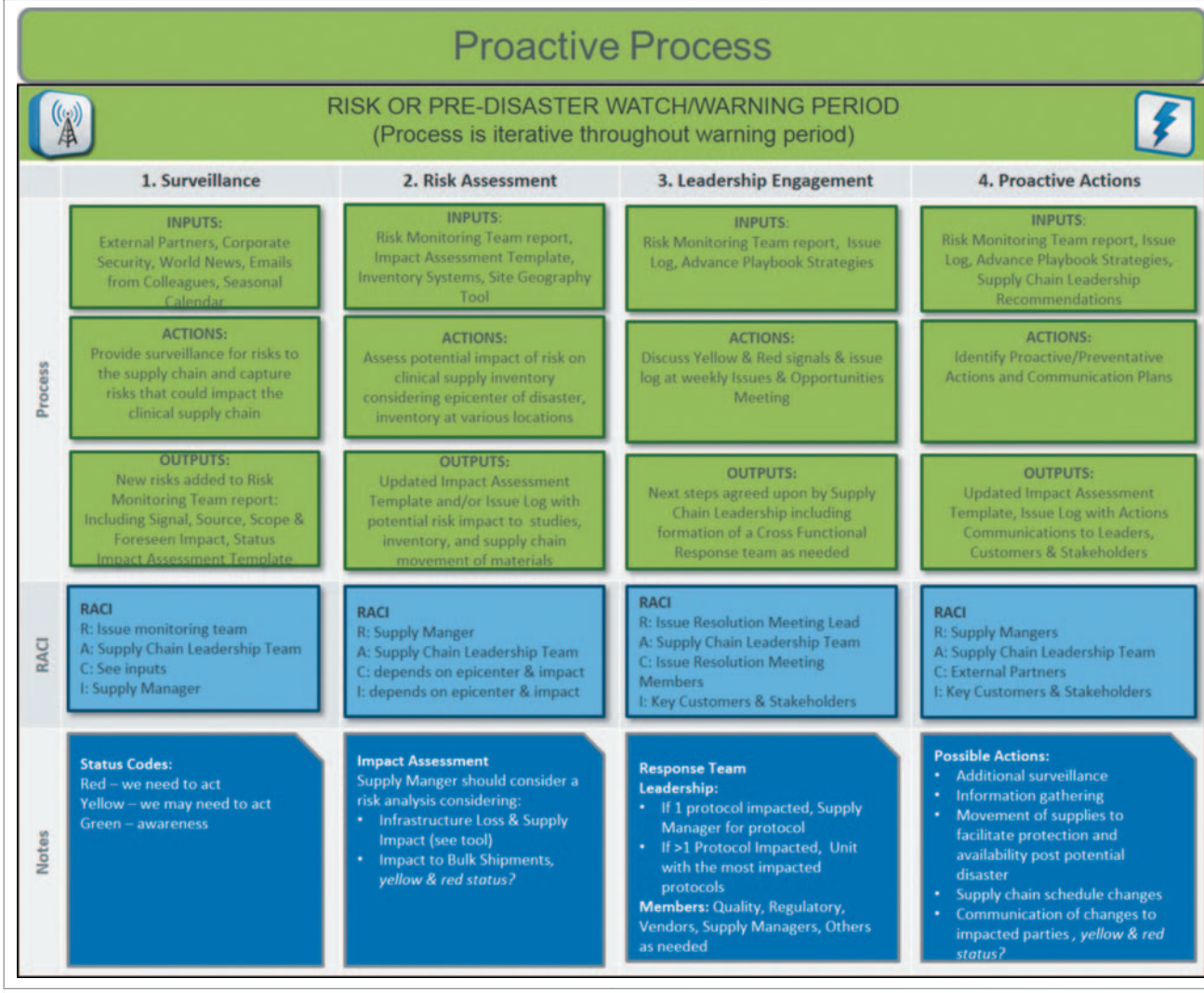
Interruption Scenarios



Source: Presher et al.

Figure 2. Examples of proactive responses to potential events that may trigger supply chain disruptions.

Planning for Disruption



Source: Presher et al.

Figure 3. The proactive response framework for clinical trials.

and documented potential risks that might interrupt development and delivery of clinical supplies. For each risk, the team numerically scored the risk based on the following three factors:

- The severity of impact should the risk occur
- The likelihood of the risk occurring
- The ability of the team to detect the signal

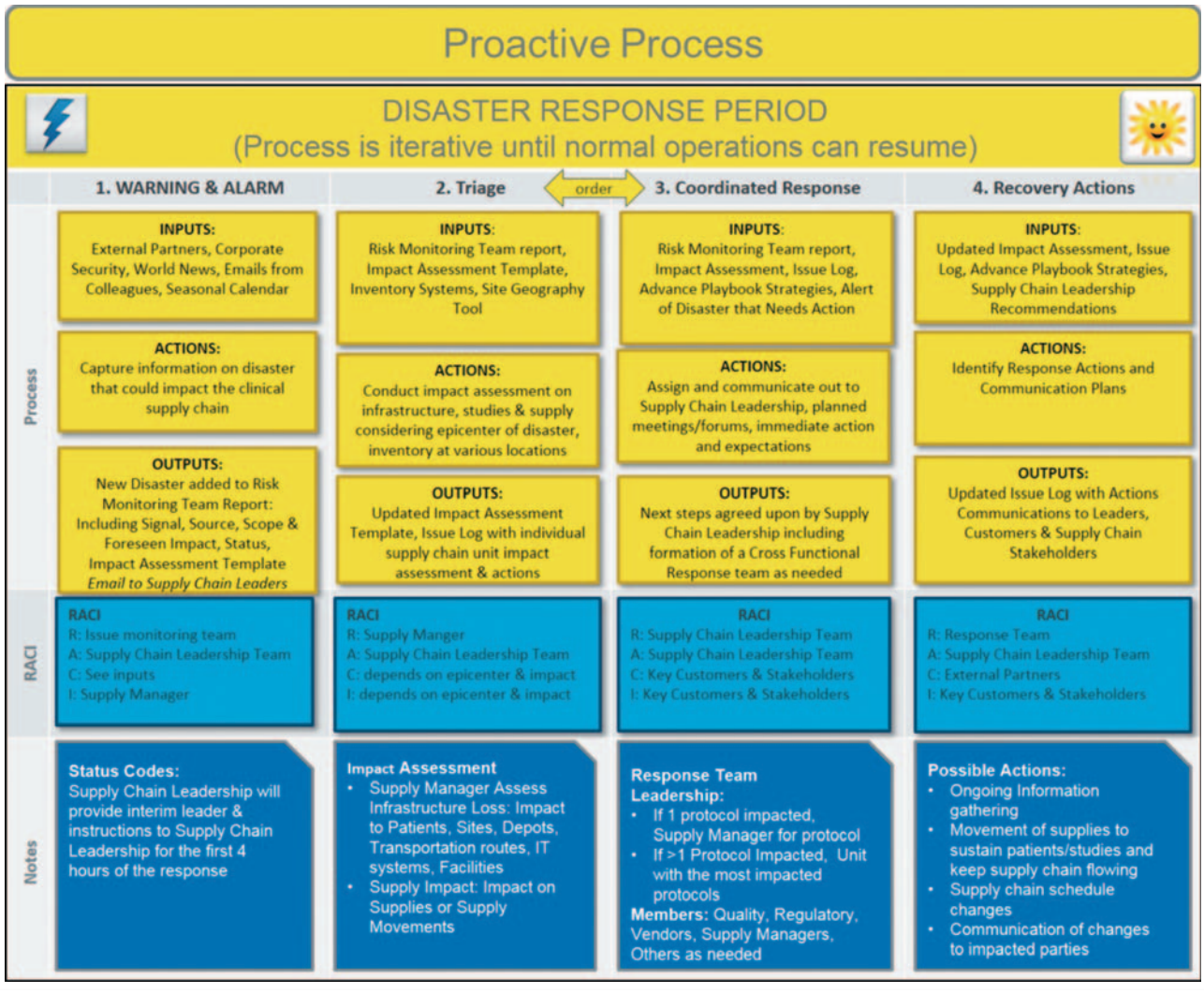
Multiplying the number scores for each of the factors above, the team identified the highest priority risks to be addressed through proactive actions when possible.

Defining proactive and reactive response processes

After completing the FMEA analysis, the team developed a framework to guide the proactive and reactive response processes. The proactive process is centered on surveillance, risk assessment, leadership engagement, and proactive actions, all of which provided a framework and risk assessment for updates to individual trial plans (see Figure 3). For example, drug supply managers aligned on necessary and important quality-focused actions, engaging quality and, if possible, reprioritizing the disposition/release schedules that might address studies or countries facing a potential risk that could interrupt supply. The team also built out supply actions, focused on assessing supply options, such as prioritizing/expediting shipments, executing site-to-site transfers (of supplies or patients). The reactive process is focused on warning and alarm, iterating between triage and response and followed up by recovery actions (see Figure 4 on page 32).

In a time of crisis, vendors will be trying to support all clients. The team also believe that, by having this proactive response, being in a

From Risk to Reality



Source: Presher et al.

Figure 4. The reactive response framework for clinical trials.

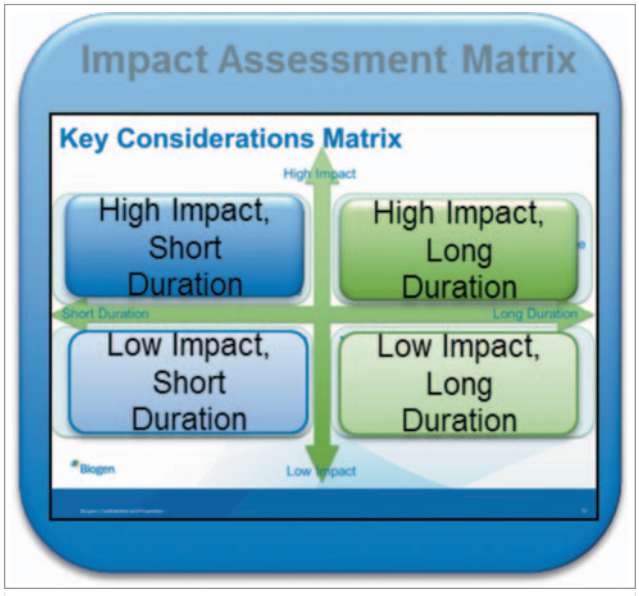
constant state of "ready" and having our response plans already 80% developed, the supply mangers will gain a competitive advantage by A) responding to a disaster before it happens and B) being first in line when a disaster actually occurs. The proactive risk mitigation procedures the team created require trial-specific plans that need to be consolidated and prioritized into a single plan.

Defining key tools and teams

To aid in the response and recovery efforts, the project team needed to establish action-oriented teams and build tools to allow the team to better plan for and respond to potential supply interruptions.

- First, and most importantly, the Early Action Response (EAR) Team was created. Its responsibility is to sift through various signals and data sources to highlight events and situations that may impact our supply chain. This activity is carried out by existing members staff. The EAR Team's sorting efforts are enhanced by reports provided by the company's global security team. Once these issues are identified—through our security team, monitoring news sites, weather information, social media, and upcoming events—the EAR Team distributes information to a larger group for general awareness or action.
- A seasonal calendar was developed. This is an Outlook resource used to track and communicate upcoming events and potential impacts. The seasonal calendar is updated by the EAR Team and discussed during regularly scheduled meetings. This tool provides visibility to weather patterns, world holidays, or major events and is intended to raise awareness of potential supply chain risks.
- A site geography tool was created. The tool allows for quick identification of sites located in a target region—where a risk event has oc-

Crisis Scale



Source: Presher et al.

Figure 5. The various event classifications that dictate how crisis managers will respond.

curred. It is used when the EAR Team dispatches an alert requiring action regarding an event posing supply risk in a certain geographic location. The tool is primarily used by the clinical supplies manager as a framework for subsequent discussions with stakeholders.

- An emergency contact for clinical sites tool was created, which serves as an escalation and hub-and-spoke communication pathway from clinical sites (through CROs) to the sponsor company and back out to sites. After initial notification of an event, the CRO business continuity team assesses impact to patients, active trials and personnel in affected region(s). This tool is used after initial assessment is made of the impact of event in particular region(s); the CRO would notify the sponsor company of issues and next steps.
- Finally, an impact assessment matrix and decision tree was created. The matrix classifies events as A) high impact, short duration B) high impact, long duration C) low impact, short duration and D) low impact, long duration (see Figure 5). Once an event has been classified, a corresponding decision tree aids the crisis manager in formulating a proactive avoidance plan or a reactive recovery plan.

Exploration of existing Biogen tools and teams

A key part of this effort was to leverage existing tools and business processes.

- The team identified a database, developed and used by our clinical operations team, that stores information on the geography of our clinical site and which studies are running at those sites. The team chose to leverage this tool and repurpose it for our initiative. So now, in a time of crisis, supply managers can determine, in a matter of minutes, the exact location of each site and the trial in which they are participating.
- The team agreed that all EAR Team updates would flow through a regularly scheduled (weekly) meeting between supply management leadership, internal/external quality, internal/external manufacturing, and other support functions. The desire was to connect the EAR updates into an existing forum rather than creating a new meeting.
- A supply chain summary table was created, which was folded into the existing supply manager peer-review process: a regular, informal review of the supply chain and supply plans for our clinical programs. This template is intended to document the supply chain vendors used for a given study and alternative vendors that can be used in the event of a disaster.

Bringing it all together

The team developed a four-step rollout, implementation, and training plan. The first step was to communicate the development of this proactive risk-monitoring plan to all of our stakeholders. The second step was training. Training included A) staging mock events to pressure test the methodology, B) including outside vendors and clinical operations, and C) performing training in waves across all invested parties. The third step was implementing the methodology into our day-to-day business operations. The final step was garnering feedback and using it to drive continuous improvement. The team recognizes that this effort will be an evolution and expects to improve with each event.

In summary, partners Biogen and Brizzey believe that this decision-making framework, which integrates real-world signals with supply planning, will allow Biogen to proactively reduce supply chain risk. The supply management organization has a team in place that is monitoring data sources for signals to identify potential supply chain impacts. The companies have built a tool that gives line of sight to major geopolitical events or natural disasters that may have potential supply chain impact.

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** The authors wish to thank Rob Pizzie of Brizzey LLC and a native son of the U.K. for his participation in the development of the process and construction of this manuscript. Thanks also to the members of the Biogen Clinical Drug Supply organization who participated in this project (Doug Meyer, Melissa Fortin, Bruce Chafee, Tala Kayyali, Meagan Ruffen, Paul Larochelle, Katie Vallone, Marissa Martinez del Campo, John Jordan, and Kate Woodcock).*

Monitoring Temperature Control Throughout IMP Supply Journey

Richard Segiel

How a single-source temperature management strategy can support a drug's quality and integrity in transit—a process as important as the destination.

PEER REVIEW

In an increasingly global clinical trials market, and with the increasing complexity of good distribution practice (GDP) and good clinical practice (GCP) regulations (*EU GDP Chapter 9; ICH GCP E6*), pharmaceutical companies must be equipped with the ability to fully track and trace the entire journey of their investigational medicinal product (IMP). However, the existing methods of collating such disparate data have made it difficult for sponsors to maintain 100% oversight of their products from manufacture to patient administration. As a result, it is becoming more of a challenge to provide assurance that regulations are being met and that product integrity has been maintained.

Sponsors recognize that during the transportation process, a drug product is exposed to a range of temperature fluctuations, leading to excursions that could impact its stability, making the treatment unfit for patient administration. It is, therefore, increasingly vital to provide a fully comprehensive picture of a product's lifecycle, in order to prove its quality and integrity and more specifically, that the drug has maintained its labeled temperature limits throughout the entire supply chain.

Temperature monitoring

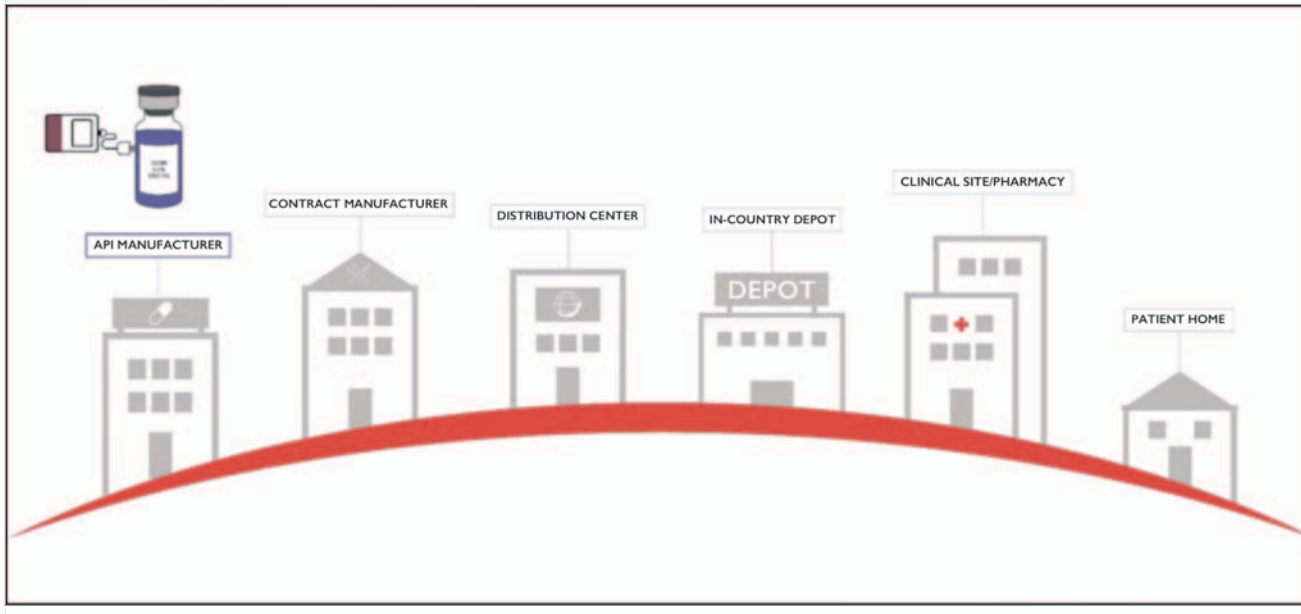
Comprehensive, GDP-compliant monitoring of all temperature-controlled material is essential throughout all shipments of clinical materials to active sites. The most appropriate method to ensure all relevant information is captured is to include a temperature monitor, which collects essential primary data, offering accurate readings that correlate to specific dates and times during transit and storage. Any temperature excursion experienced can support decisions on the product and can be easily associated with the transit route. This can enable retrospective comparison and analysis of the methods of transport chosen, offering a level of control and visibility that provides information to support decisions, processes that are followed, and how future material should be shipped and stored.

The existing method of collecting and manually assessing this essential temperature data often means managing multiple vendors and software applications. The analysis of this data is hugely valuable; however, it is also labor intensive and time consuming, issues that have the potential to impact study timelines or cause interruptions in the supply chain. Single-source temperature management systems offer a more sophisticated solution to house all collated data on one single platform in the most efficient way possible. Across the entire clinical supply chain, the speed at which the information is available offers data for interrogation and instant analysis, empowering companies to quickly put logistics strategies in place to reduce risk. This single-source also better aligns companies with new regulations concerning patient safety and saving money, time, and lives.

The supply chain journey

An increasing number of sensitive and sophisticated pharmaceuticals are required to be maintained at a controlled temperature. For example, in 2016, 75% of the shipments that Almac Clinical Services managed required temperature controls—up from 25% just five years earlier. These new temperature requirements are proving to be a real challenge for drug manufacturers. Typically, developing a supply chain strategy has been a complex process involving a sequential series of decisions, including:

Data Bottleneck



Source: Segiel

Figure 1. Unrelated data silos across the clinical supply chain.

- **Obtaining the product stability data.** These are specific details, including mandatory temperature storage range, any allowable excursions, optional "excursion budget" (the product may withstand multiple excursions up to a certain cumulative limit), and other pertinent information relating to the product. Trials may be early in the development phase and all data not fully available.
- **Mapping the journey of the product during transit to destination**, including identifying any specific challenges associated with the footprint of countries that will be involved in the trial, the shipping lanes needed, and the various storage facilities required.
- **Establishing the product's varying requirements and ensuring adequate facilities throughout the entire distribution chain.** This will guarantee complete compliance throughout. The varying complexities and environments associated with the supply chain are challenging and every product is unique, particularly when the trials being conducted are truly global. Every shipment makes its way to patients via an array of different storage and handling conditions (e.g., a diverse range of phase change shippers, temperature monitors, different couriers, and depots). Each mode of transport, period of storage, and change of hands has the potential to expose the packaged product to temperature changes. Clinical sites offer a variety of storage facilities and conditions, making it harder to maintain control over the drug product. In addition, holding all sites to a common standard is very difficult. The personnel responsible for handling the product must be adequately trained to ensure they are packing, receiving, unpacking, and storing the material in the most compliant way. However, this often varies and human error can also impact the product.

Reporting temperature data on each stage, location, and handling across multiple, unrelated databases means there is no one central source providing a complete oversight of the temperature data throughout the product lifecycle, resulting in unrelated data silos across the entire supply chain (see Figure 1).

It is considerably complex to address all of the planned factors. But, of course, even with the best-laid plans, there is the potential for an unplanned event that could easily jeopardize the product's condition. Traffic congestion between an airport and a site could delay delivery until a site reopens after closing for a weekend. Material could be removed from a plane and sit in a store for hours. Customs officials could open shippers and remove the temperature monitors. Each change in location and stoppage throughout a product's journey will impact temperature conditions caused by exposure to varying climate changes and conditions.

It is, therefore, essential for supply chain managers to plan a product's path, taking into consideration the risks and costs associated with the different climate, timelines, and regulatory hurdles presented by varying modes of transport (air, sea, or land), shipping lanes, package options, and storage locations, and they must implement a suitable strategy to deal with each planned event throughout the journey. This strategy must be robust enough to prove regulatory compliance and drug supply assurance to the patient, while also reducing the strain at sites and allowing improvements to be made in the future.

The clinical site

Clinical sites are involved in much more than dosing patients with the IMP. They can manage tens to hundreds of protocols with various sponsors, who all require completion of a host of documentation, reports,

and other tasks. Today, due to tightening of regulations on temperature monitoring, some sponsors are requiring sites to place separate temperature monitors within controlled storage (2-8oC, 15-25oC, -20 oC, etc.) and download the readings monthly. Sponsors are attempting to comply with these regulations to ensure that IMPs are stored within the allowed limits, but doing extra monitoring can be challenging for sites.

Storage compliance of IMP can also present hurdles (e.g., validated refrigeration). With this burden comes the associated struggle for the sponsor to execute a successful site-level monitoring plan, which is almost always dependent on staff diligence and adherence to agreed expectations.

Finding an auditable and GCP-compliant platform that can support and ease the data collection burden on these sites and their individual staffs—and which facilitates excursion management and recording of storage temperature history—can be the solution. Combining that with adjudication staff who can provide an immediate response to reported excursions, make a decision about product viability, and determine a course of action, especially if the situation will impact patient treatment, is the most suitable strategy for clinical site compliance.

Data oversight

Mitigating against risk is vital and, while risks cannot be eliminated, fully assessing transportation and temperature management is the first step. Fine-tuning product stability data is the next.

Most quality assurance departments manually assess and evaluate each out-of-spec temperature excursion as and when it occurs. Clearly, due to the nature of this process, mistakes happen and efficiencies are low, causing potential delays. If a system could track all excursions cumulatively for a particular product lot, shipment, or kit to document the product history, as well as hold predetermined excursion allowances based on the product stability, quality assurance could make product quality evaluations more accurately and quickly because the decision-making and justification is performed up front.

For products with appropriate temperature stability profiles, the data can be used to create predetermined allowable excursion criteria and support a more flexible approach to product evaluation. This could minimize the need to discard material that may be viable due to temperature excursions. For example, a product labeled with storage conditions of 2-8°C may actually be stable at 9-15°C for 180 minutes and at temperatures of 15-25°C for 30 minutes before the product is deemed not viable. Giving quality assurance groups predetermined and visible criteria for excursion adjudication allows for a robust and justifiable process for product disposition that is based on data and risk to the patient.

Advances in temperature-controlled shipping systems, courier services, airline infrastructure, and services are all enabling significant improvements in temperature control during transit. This offers the best physical infrastructure for distribution, providing the same robust performance and level of assurance to that of the temperature-controlled warehousing that the industry employs today. However, in the same way that the industry would not operate temperature control warehousing without collecting and reviewing the data on a regular basis, so too should we be as diligent with regards to the data that is, and can be collected as the product moves throughout the clinical supply chain.

While this physical infrastructure has historically been the best practice approach for drug manufacturers, with increasing regulations (both in transit and in storage), this is no longer solely sufficient to achieve compliance. The only way to prove this is to lead with a data-driven strategy, using a platform that provides a complete view of the physical supply chain and which facilitates robust data collection and analysis across a universal data repository. Moreover, the platform should be flexible to support what is a varied supply chain of numerous stakeholders (e.g., insulated shipping systems, temperature monitors, distribution centers, couriers, and clinical sites).

By consulting data on the end-to-end supply chain and each touchpoint of the product's journey—in transit and at the clinical site—it is then possible to adopt a proactive approach to distribution that drives improvements and regulatory compliance, lowering the risk of unplanned temperature excursions while providing controls for planned excursions—when products are intentionally removed from ideal conditions to allow for processing. A platform that also integrates with interactive response technologies (IRTs) is a best practice. This allows material that has undergone an excursion to be quarantined while the excursion is reviewed, and can trigger resupply shipments to avoid stock-outs.

Manufacturers can gain added assurance by working with a team of dedicated temperature experts, who can support in-depth data analysis, creating an audit trail of each shipment, analyzing problems, and ultimately learning from and building on experience. For global clinical trials, this requires having global staff available 24 hours a day across different time zones. With this data-driven approach, drug manufacturers can create a better global supply chain with full assurance that their physical infrastructure is working and that their drug product is safe to administer to the patient.

Conclusion

In order to ensure companies are minimizing risk associated with shipping temperature-sensitive material from origin to destination in an ever evolving market—with tough GDP and GCP regulations in place to protect the patient—it is important to combine valuable data analysis and assessment with appropriate distribution methods. The best supply chain strategy needs both the physical and the data components, in order for a complete temperature record to be available. Combined on one platform and supported by a temperature management expert team, this data-driven strategy will form the foundation for in-depth data tracking and analysis, driving decisions and improvements as well as management of different stakeholders and the clinical sites.

As technology advances, companies must also take a proactive approach to avail themselves of new solutions offering more efficient and effective methods of temperature management. This not only provides sponsors with the opportunity to maintain their competitive advantage by saving time and money associated with distribution, but also enables them to ensure patient safety through a compliant approach applied throughout the entire shipping process. This strategic planning will essentially ensure that the product's journey is as important as the destination.

Richard Segiel *is Vice President, Business Development, Almac Clinical Services*

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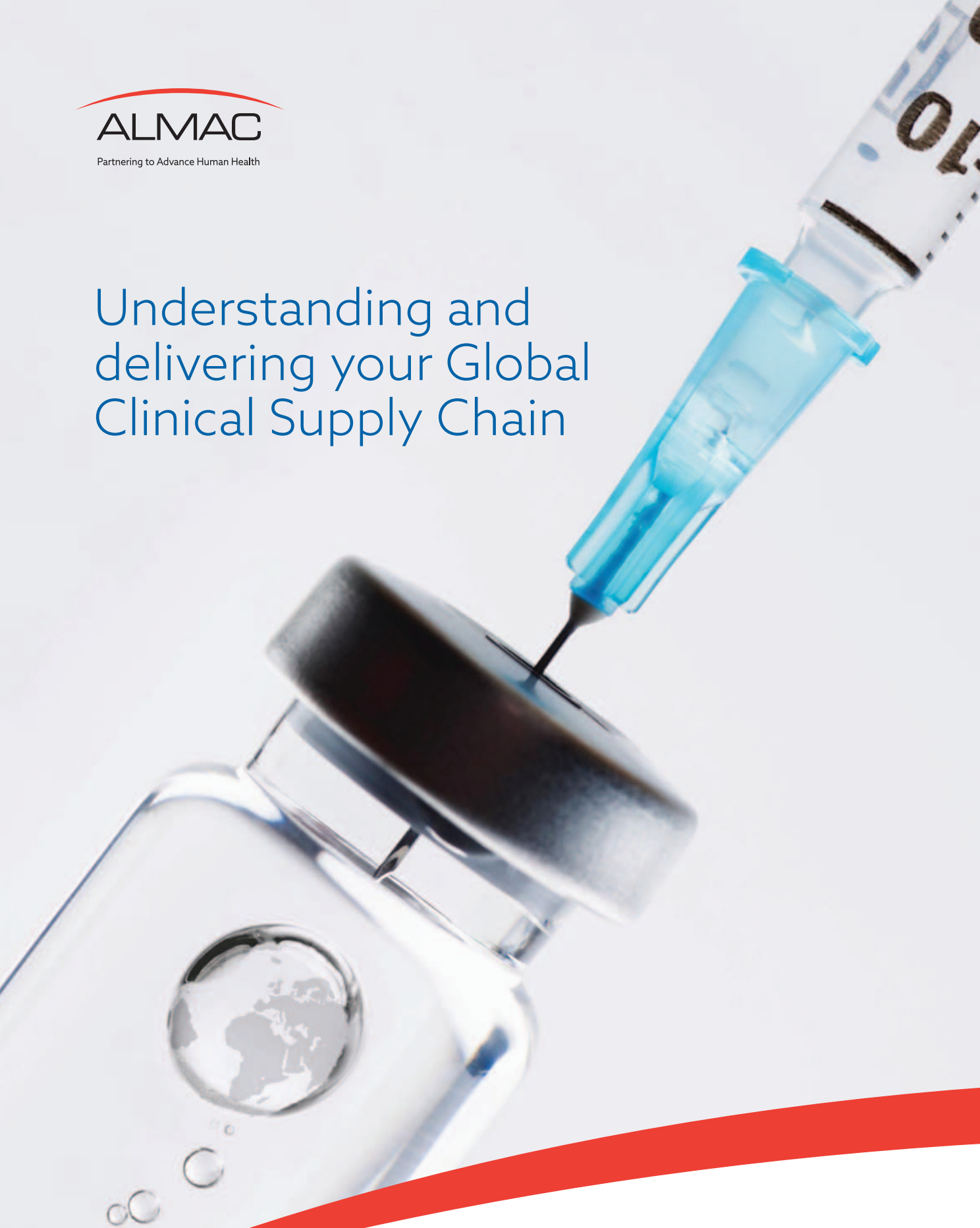

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The Success of Cell Therapies Will Depend on Automation

For a life-altering treatment that may cost hundreds of thousands of dollars and cannot easily be replaced, is improper thawing truly worth the cost?

Rolf Ehrhardt, MD, PhD
CEO of MedCision

Cell therapies are among the most promising new drug therapeutics since the rise of monoclonal antibodies. Globally, thousands of clinical trials based on live cell therapies are already taking place, with some analysts predicting a market value of $180 billion for this industry within the next 15 years. The pace of innovation and the opportunity to improve clinical outcomes for oncology, stroke, and heart attack patients, to name a few, are truly staggering.

To give cell therapies the best chance of success, now is the time to ensure that every protocol or technology involved in delivering a live therapeutic to a patient meets the highest standards of integrity, efficacy, and consistency. It is imperative to demonstrate that we, as a community, can standardize, document, and scale up best practices for optimal patient care. As part of this process, it behooves us to take a hard look at each step in the production and delivery of cell therapies, and find ways to reduce the potential for human error. Automation will be key to this effort, as it improves efficiency and mitigates risk.

As an example, let's look at something that conceptually sounds rather simple: cell thawing. This is typically the last step before a cellular therapeutic is injected into a patient. Without automation, the thawing process is unstandardized, undocumented, and prone to contamination. Technicians tend to improvise with cell thawing precisely because it appears at first glance to be basic; running vials or cryobags under warm water, floating them in a water bath, or even rolling vials between their hands. Even with the most scientifically validated methodology, using water baths is notoriously risky due to potential bacteria/fungi infection, and risk of contamination via microscopic tears in cryobags, or leaking cryovial caps.

The highest concern is that these unstandardized thawing methods can lead to decreased function of live cell therapy products by reducing viability and proliferative capacity or by shifting the ratio of cell types in a mixture. For a life-altering treatment that may cost hundreds of thousands of dollars and cannot easily be replaced, is improper thawing truly worth the cost? It's all too easy to imagine these problems ruining a clinical trial that might otherwise be quite successful if the therapeutic were properly handled.

At MedCision, our scientists have a passion for eliminating human error. Based on demand from clinical trial companies and other organizations involved in the cell therapy field, we've developed an automated technology to ensure standardized, carefully controlled thawing of live cell therapies in a range of cryobags or vials. Compared to a water bath, this approach results in a highly reproducible thawing profile, along with higher viability and cell recovery for improved long-term function.

Making things as simple as possible is our mantra for any kind of clinical automation, and it's a good guiding principle for anyone looking to innovate this industry. Our automated cell thawing technology is highly standardized, incorporating advanced sensors to detect phase change and complex algorithms that calculate a precise optimal thawing time for each unique drug. The end user, however, never sees any of this complexity. Instead, a simple design allows a one-step operation that can be accomplished with little to no training.

Cell thawing is just one step in the post-manufacturing chain of custody for live cell therapy products; there are many other areas where automation will be essential to improving reproducibility and robustness for delivering these high-value live treatments. I encourage the cell therapy community to question every protocol involved in shipping, storing, and administering these therapies, and to identify other components in the process that would benefit from more standardized methods. Optimal approaches typically include instruments or workflows in which parameters and processes can be fully locked down so they perform the same way every time, regardless of user or conditions.

Through automation we can incorporate software for recording and tracking data, which, in turn, helps ensure regulatory compliance, chain-of-custody reporting, and, ultimately, more predictable treatment outcomes. Greater consistency will also reduce the overall cost of therapy, resulting in a win-win situation for everyone.

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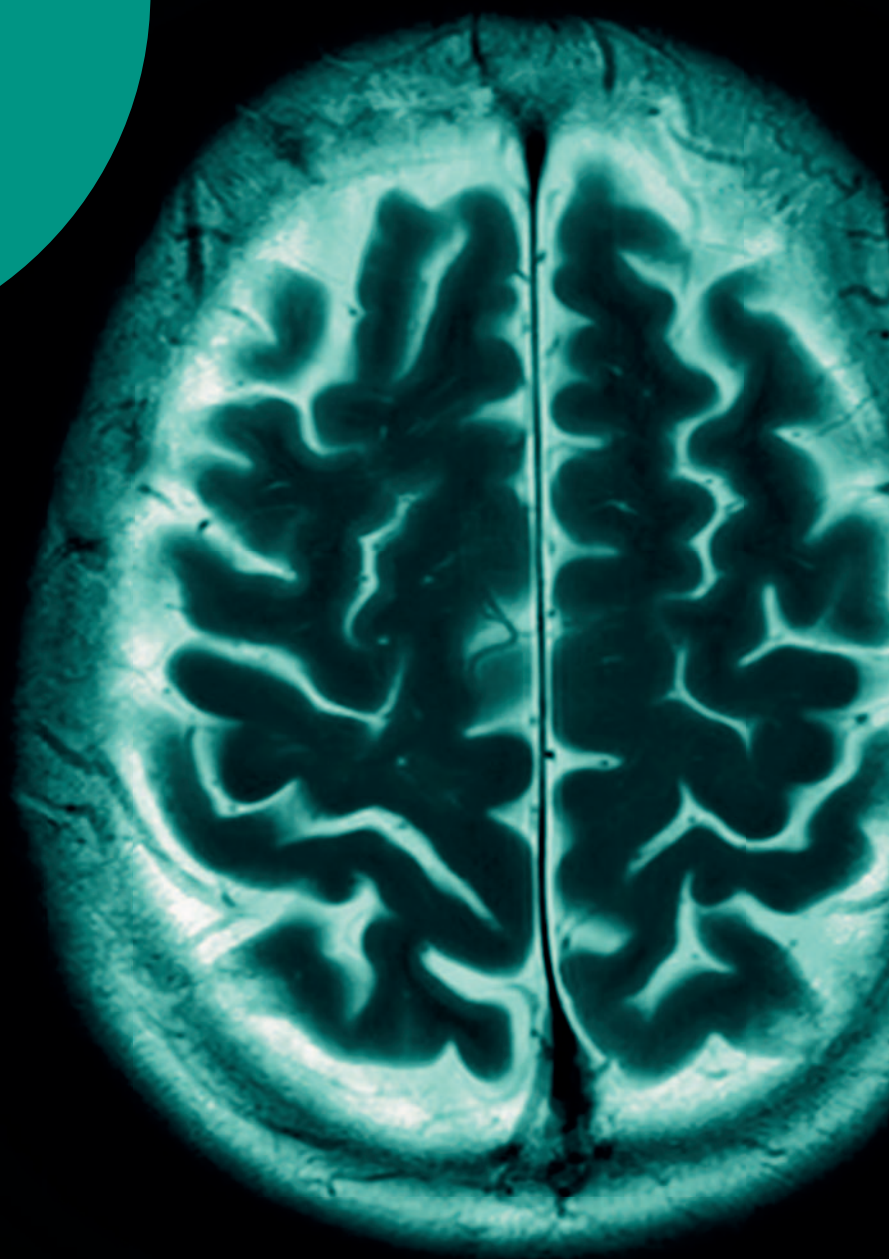

The use of medical imaging in clinical trials enables improved decision making, increased efficiency, and can reduce trial costs in the long run.

Working with ICON offers the expertise of an industry-leading medical imaging specialist combined with the strength of a global CRO.

Contact us today to discuss the benefits of including medical imaging in early development.

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