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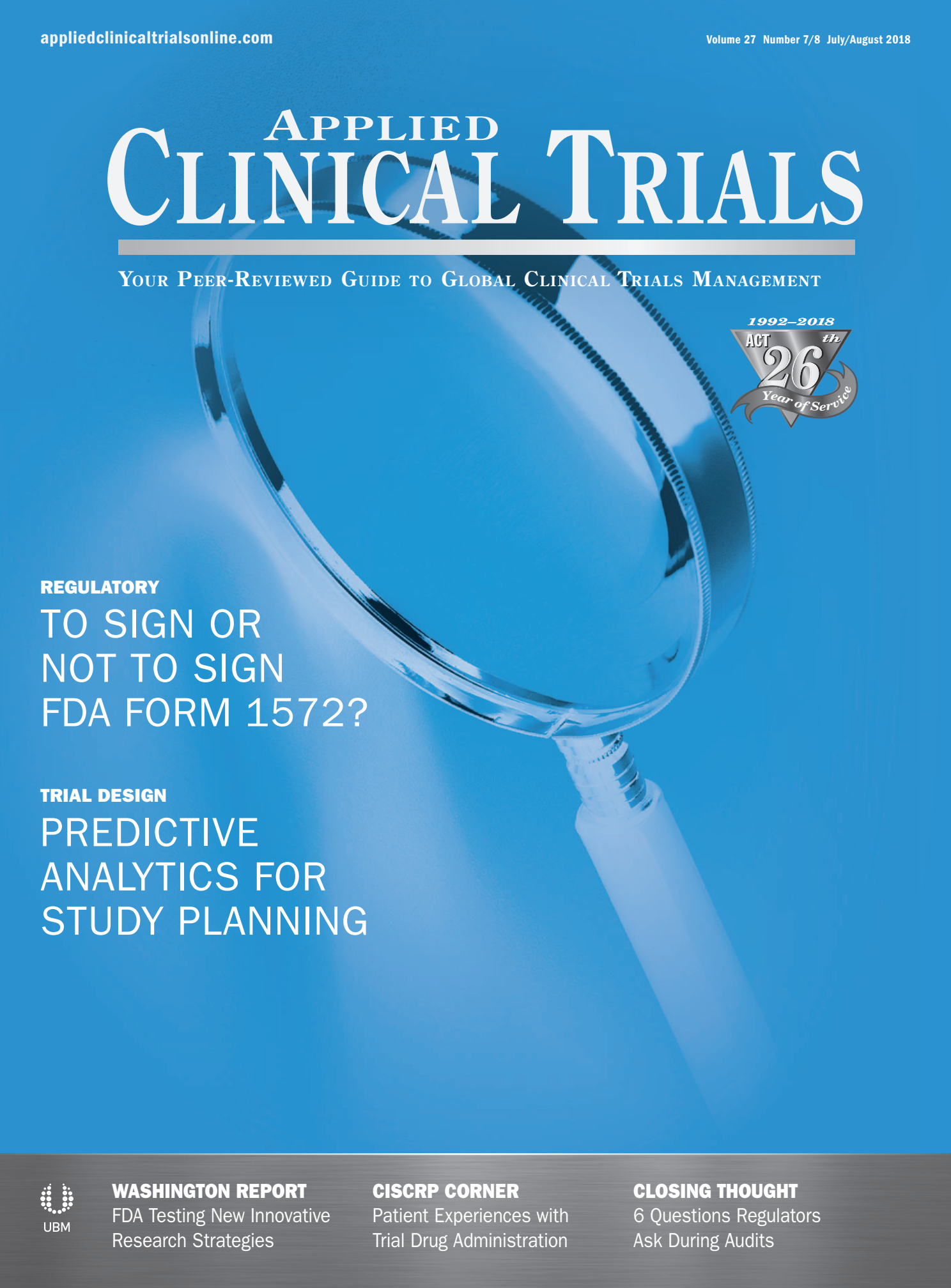

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A Glimmer Is All That's Needed for Alzheimer's

LISA HENDERSON
Editor-in-Chief

Last month's Alzheimer's Association International Conference (AAIC) 2018 heralded many announcements, including the mixed reception around Phase II trials results from Biogen's Alzheimer's drug BAN2401. Like many treatments in AD, it addressed build up of amyloid plaques in the brain. However, many drug failures in that area, as well as Pfizer's exodus from Alzheimer's and Parkinson's research early this year, has led to investors and scientists to reevaluate the plaque theory.

In the week prior to AAIC, Bill Gates announced a $30 million "venture philanthropy" fund to develop novel biomarkers for the early detection of Alzheimer's disease and related dementia. One of the reasons for the shaky AD drug development is the inability to find patients in early stages of Alzheimer's.

Edward I. Ginns, MD, PhD, medical director, neurology, for Quest Diagnostics, said, "When we see patients at the point of clinical identification, the brain is pretty much out of resources. It's unlikely that neurons that are dead or non-functional will be treated at that late stage." To that end, Quest Diagnostics wanted to identify patients with cognition problems earlier. They developed CogniSense, a cognition test that is available as an app for the iPad and given in the primary care doctor's office. "Physicians need the tools to rule out reversible causes of mild cognitiive impairment, and then to be able to refer others out to specialists, when needed," said Ginns.

With over five million Americans presenting with some kind of cognitive impairment—not just Alzheimer's—the healthcare system, as well as individual resources, are becoming unsustainable. With CogniSense, the patient can take a baseline test, with results stored in the Quest lab-ordering platform, Care360. Subsequent tests can be ordered to monitor and track a person's cognitive function, as the information is now part of the patient's medical record. By coming to cognition from the front-end, there is potential that Alzheimer's, as well as other cognitive disorders, can be identified and treated earlier, with potential discovery candidates coming from patients' lab or cognitive data.

In March, the National Institute on Aging and the Alzheimer's Association released a new framework which proposes that biomarkers, not symptoms, could be used to assess AD for research. While not currently intended for clinical use, this new framework is expected to facilitate better understanding of the disease process and the sequence of events that lead to cognitive impairment and dementia.

Ginns noted when he was an NIH researcher and discovered Gaucher disease, researchers now think, 20 years later, that those with Gaucher are five-times more likely to have affects of Parkinson's disease. With biomarker and early identification taking a lead in the form of the NIH framework and Bill Gates' influence, as well as developments in current Alzheimer's drugs, and through collaborations, Ginns hopes Alzheimer's science speeds up. While it appears early on that BAN2401 wasn't the spark needed for Alzheimer's research, Ginns is convinced once there is a breakthrough, that glimmer of hope, it will truly open up development on many levels—diagnostics, clinical care, and medications.

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PEER REVIEWED

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Natalia Buchneva

Exploring that pivotal question for clinical investigators, sponsors, and global CROs.

FEATURED

NEWS AND ANALYSIS

COMMENTARY

WASHINGTON REPORT

SCIENTIFIC ADVANCES REQUIRE INNOVATIVE CLINICAL RESEARCH MODELS

FDA is testing a number of strategies to streamline research and regulatory oversight of new cancer treatments, cell and gene therapies and more targeted medicines, with an eye to advancing innovative methods for developing protocols and evaluating research data in multiple drug categories. FDA Commissioner Scott Gottlieb told the American Society of Clinical Oncology (ASCO) in June that new steps to accelerate cancer R&D will "make the entire continuum of drug development more efficient," lowering costs and promoting innovation, (see bit.ly/2t13eZj)

With more than 500 cell and gene therapies in early development, and nearly 20 designated as Regenerative Medicine Advanced Therapy (RMAT), FDA is looking to novel clinical trial designs to advance new treatments. The agency issued six draft guidances in July that provide scientific advice on developing novel treatments for hemophilia, retinal disorders, and rare diseases, plus long-term follow-up and manufacturing (see bit.ly/2NY6CMJ) Because these products target devastating diseases, FDA expects to approve promising therapies based on surrogate measures, with required post-market studies that use registries and real-world patient evidence to document continued benefit or detect safety issues.

Early advice

To speed the development of cancer therapies, FDA's Oncology Center of Excellence (OCE) is testing new strategies for improving the evaluation of clinical data in applications. One pilot establishes a "real-time oncology review" (RTOR) process. The program allows sponsors to share with FDA bottom-line data from a clinical trial soon after locking the study database. Applicants gain early feedback on data quality and how best to analyze results to answer important questions, and FDA staff is able to pre-review the data and address regulatory questions before formal review. When the sponsor files its new drug application, an agency review team familiar with the product will be able to conduct "a more efficient, timelier and thorough review," Gottlieb explained. He estimated that this approach should free 10% to 30% of reviewers' time, leaving more opportunity for staffers to engage with product developers. In July, FDA used the RTOR process in approving an expanded indication in less than one month followingreceipt of the application for Novartis' Kisquali (ribociclib) for advanced breast cancer.

Another pilot is testing the use of a new template for assessing submissions for supplemental applications. This review tool enables FDA reviewers and sponsors to note areas of agreement and disagreement and additional findings directly on the review document, instead of creating separate reports that repeat the same data. This "more agile platform" for reviewing data should reduce the administrative burden on FDA reviewers and help them focus on critical results and analyses. The end result should be a single, annotated application ready for advisory committee review. If successful, Gottlieb envisions expanding this approach to original drugs and biologics in other treatment areas.

Patient perspectives

Initiatives to advance precision oncology treatments were further discussed at a June workshop on clinical outcomes assessments in cancer clinical trials, co-sponsored by FDA and ASCO. OCE leaders and research experts examined new approaches for assessing patient-reported outcomes (PROs) in cancer trails, different systems for developing PRO strategies, and FDA policies for using PRO data in regulatory review.

At the same time, FDA published the first of several guidances designed to further utilize patients' perspectives in drug development. An initial draft advisory recommends methods for collecting patient data in clinical trials (see bit.ly/2t0iG8e), and additional guidances will provide more detail on using interviews and survey information, on identifying issues most important to patients, and in selecting patient-focused study endpoints. The overall goal is to map out sound methodology for collecting patient input, so it provides data that can inform regulatory decisions.

A related goal is to encourage more patient enrollment in all clinical studies, and FDA plans to roll out guidances with strategies for including more under-represented patients in trials. Efforts to promote broader inclusion criteria are seen in a recent guidance that supports studying adolescent patients in adult oncology trials, based on evidence of similar disease occurrence and toxicity in both adults and adolescent age groups (see bit.ly/2MxcRHg). FDA wants trials to examine more elderly subjects and patients with poor performance status and comorbidities and to address geographic and financial barriers that prevent participation, possibly by advising sponsors to conduct studies in the communities where patients live.

The larger goal for FDA, Gottlieb says, is to create a regulatory system that approves new cancer drugs and other breakthrough therapies without large, prospective, randomized clinical studies to prove overall survival. More targeted therapies can demonstrate high benefits in studies on smaller cohorts of carefully selected patients using relevant surrogate endpoints, and more pragmatic clinical trials at the point of care will be able to harness the vast amount of data generated by routine patient interactions.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

6/20/18: Major Depressive Disorder: Developing Drugs for Treatment

6/13/18: Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis

6/4/18: Considerations for the Inculsion of Adolescent Patients in Adult Oncology Clinical Trials (draft)

5/31/18: Complicated Urinary Tract Infections: Developing Drugs for Treatment

EU REPORT

DOES THE EU REALLY CARE ABOUT HEALTH POLICY?

Even when the UK ceases to be a member of it, the 27-country European Union will still be among the most powerful and richest trading blocs and markets in the world—an important terrain, therefore, for any established players in healthcare, or any rising stars. But how much does the EU really care about health, and about the infrastructure that is a precondition to successful healthcare and healthcare innovation?

A couple of key developments in early summer offer some clues, some hints, as to the answer. Exhibit A is the EU's current convulsion over its next long-term budget, and the priorities that this indicates between now and 2027. Discussions are reaching a crescendo in the EU institutions and among the thousands of competing lobby groups over who should get what from the roughly $1.5 trillion up for grabs.

On the face of it, health isn't in line for a lot—perhaps little more than $400 million. Amid the myriad budget headings—ranging from humanitarian aid to agricultural subsidies and border management to security and defense—health barely features at all, and when it does, it is only as one component among many others in sub-programs with broad-ranging titles such as Investing in People, the European Semester, or Horizon Europe.

The European Patients' Forum has pointed out that the funding specifically earmarked for health is lower than at present, despite "the formidable common and increasing challenges that European countries are facing" in healthcare. Not much of that will go toward boosting medicines development, either: the focus will be on health promotion, disease prevention and protection, focused largely on combating smoking or alcohol abuse. The two latest calls for tender under the current program are offering more than $200 million for "Implementation of best practices to promote health and prevent non-communicable diseases and to reduce health inequalities"—hardly topics to set the pulses racing of developers of innovative therapies.

The EU's research program, with a proposed budget of $100 billion to cover fields as diverse as aeronautics, information technology or energy, envisions some allocation for health with the emphasis on the treatment of rare diseases, orphan drugs, and preparedness for pandemics. The European research-based drug industry has offered a muted welcome, accompanied by a plea for a big share for medical innovation.

But these are just proposals at present, and not everyone is pushing for more spending on health, or for spending to be directed to innovative medicines. Non-governmental organizations are chorusing their concern over a failure to target global health challenges, and what they see as a dangerous shift toward a pro-industry focus in the proposals. "When issues of public concern and that are reliant on public investment, like health research, are pitted against private sector interests, there will only be one winner—and it won't be the billion people living today with a poverty-related disease," said Cecile Vernant of the German Deutsche Stiftung Weltbevoelkerung charity, urging a fight-back against what she depicts as excessive generosity to drug innovators.

Exhibit B in this brief analysis was a paper discussed in June by the national health ministers who constitute the EU Health Council. This paper, entitled "The Future of Health in the EU," is intended to prompt ministers to "contribute to shaping the political agenda in the health field at European level"—an apparently curious idea, after more than 60 years of the EU and more than a decade of EU health policy. But it exposes the reality that health policy—such as it is in the EU—is still adrift, still incoherent, blown hither and thither at the whim of circumstance rather than springing from a clear and agreed strategy. The EU treaty provides only limited powers for the EU in health, leaving much of it to national authorities—and the indifference that this has bred about EU engagement in health is all too obvious.

As Council officials said in launching the discussion, there is currently intense debate on the future of all EU policies, and if there is to be a health policy it needs to be seen against "the rapid development in fields such as eHealth, pharmaceuticals, and medical devices." But the paper itself, authored by Bulgaria, the country in the rotating chair of the health council for the first half of 2018, hardly aims high in its reflections. "Where harmonization cannot be the solution, cooperation can be a bottom-up way to identify best practices and make improvements," it boldly suggests.

The paper's main thrust appears to be to deploy EU health policy as a brake to prevent private industry dominating the public health agenda. While the paper acknowledges "the role of industries in generating growth, jobs, and revenues," it insists health policy should support "delivery for patients," and "act as a broker, whenever public and private interests diverge." It concludes by posing two questions to ministers: how can member states shape the agenda on health and respect the EU treaty limitations, and which areas should be the focus for action?

Even before the health ministers' answers are available—if indeed they choose to answer at all—it seems grimly clear that health is going to continue to struggle to be taken at all seriously in EU policy formation.

— Peter O'Donnell

EMA NOTES

FIRST CAR-T RECOMMENDED FOR APPROVAL IN EU

The European Medicines Agency (EMA) has recommended the first two marketing authorizations for chimeric antigen receptors (CAR) T-cells medicines in the European Union. Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), advanced therapies for blood cancer, belong to a new generation of personalized cancer immunotherapies that are based on collecting and modifying patients' own immune cells to treat their cancer. Kymriah and Yescarta are also the first medicines supported through EMA's PRIority MEdicines (PRIME) scheme to receive positive opinions from the Committee for Medicinal Products for Human Use (CHMP).

CISCRP CORNER

PATIENT EXPERIENCES WITH CLINICAL TRIAL MEDICINES AND INSTRUCTIONS

This article is the fourth in a series on the results from the Center for Information and Study on Clinical Research Participation's (CISCRP) 2017 Perceptions & Insights Study. Nearly 12,500 people worldwide responded—including the public, patients, and study volunteers—and provided valuable insights into opportunities to improve global education, outreach, and engagement.

Sponsors have been investing heavily in patient engagement initiatives to reduce study volunteer participation burden and improve participation experiences. Optimizing the administration of clinical trial medicines and their accompanying instructions are critical means to establishing positive volunteer experiences, better compliance, and higher retention rates. The 2017 Perceptions and Insights (P&I) Study offers insight into opportunities for sponsors to optimize clinical trial medicine kits.

The 2017 P&I Study included 2,194 global clinical trial participants. These patients shared their experiences with different types of investigational medicines and accompanying instructions, their ability to remember to take their investigational medicine, and the support they received from site staff when asking investigational medication-related questions. Bottled medications were used most frequently by patients (23%), followed by blister packaging (15%) and pre-filled syringes (11%). The method of administration varied across regions. European patients reported the lowest use of bottled investigational medications (9%), and those from South America and Africa reported significantly higher use of topical investigational medications (17% and 19%, respectively) compared to approximately 5% in other regions.

In aggregate, experiences with investigational medicines and medical devices were generally positive. The majority of patients felt remembering to take and administering medicines was "very easy" (74% and 76%, respectively). Instructions accompanying investigational medications were also described by most as "very easy" to understand (74%), and the majority of patients thought site staff answered medication-related questions "very well" (68%). However, areas of opportunity to improve experiences and increase compliance emerge when the methods of administration and different patient populations are examined more closely.

Challenges by method of administration

Overall, investigational medicines in bottles proved to be the least challenging for patients when compared to other methods of administration. In the latest study, patients reported bottled investigational medications to be the easiest to administer (84% "very easy") and to remember to take (80% "very easy"), followed by investigational medication in blister packets (74% "very easy" to take, 73% "very easy" to remember).

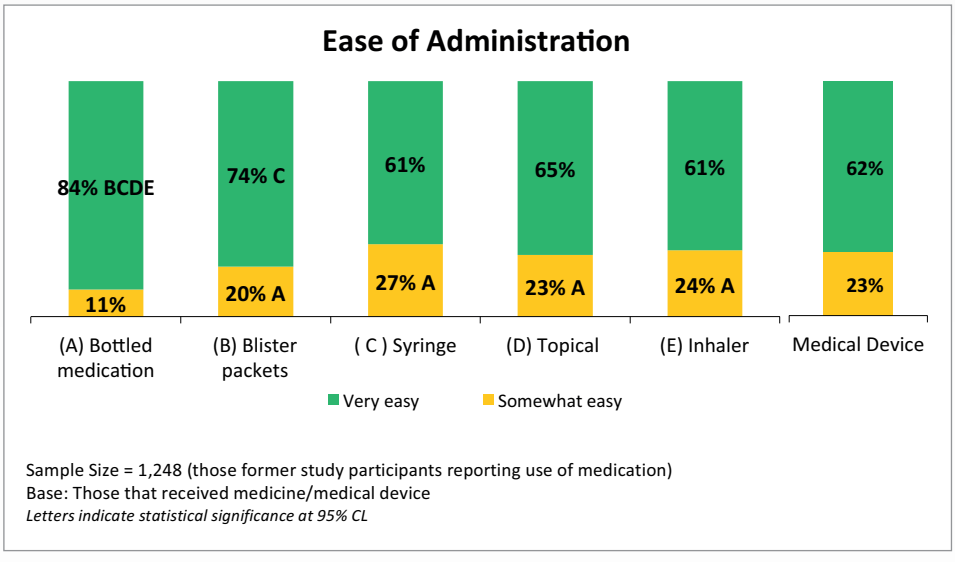
Patients whose medicines were more involved (i.e., administered via syringe, inhaler, or topically) expressed more difficulties, and the need for increased education and instruction was additionally noted. These investigational medicines were less likely to be considered "very easy" to administer by patients (see chart) perhaps because these methods are typically more complex and may cause some discomfort. These patients were also less likely to feel their medicine instructions were easy to understand (63% syringe, 62% inhaler, 59% topical "very easy" to understand) compared to patients receiving their medication in bottles (81% "very easy").

Challenges by specific patient populations

Difficulties specific to certain patient-subgroups also illustrate the need for increased education and support for particular populations.

Experiences with investigational medicines generally improved with age. Those 18 to 44 years old were significantly more apt to have difficulties administering their investigational medicines (16% "somewhat/very difficult") compared to patients 45 or older (4% "somewhat/very difficult"). Younger patients were also less likely to feel site staff answered their investigational medicine-related questions well and found instructions to be more challenging to understand compared to older patients.

Perhaps due to increased work or family commitments, younger patients additionally struggled to remember to take their medication (19% "somewhat/very difficult") compared to older patients (3% "somewhat/very difficult"). Notably, in this most



Sample Size = 1,248 (those former study participants reporting use of medication)
Base: Those that received medicine/medical device
Letters indicate statistical significance at 95% CL

CISCRP CORNER

recent study, a higher proportion of younger patients stated they would have liked text messaging to have been used during their clinical trial for reminders. This may offer an innovative way to improve compliance and better engage a younger generation of trial participants.

Level of education also impacted experiences. Among patients with a primary level of education, less than half found administration to be "very easy" (49%) compared to patients with a higher education level (75% "very easy"). A similar pattern emerged when looking at understanding of investigational medicine instructions; 19% of patients with limited education described instructions as "somewhat" or "very" difficult to understand compared to patients who had a higher education (6% "somewhat/very" difficult).

Patients identifying as Hispanic or Asian also reported increased challenges with investigational medicines. Only 43% of Hispanic patients indicated investigational medicine administration to be "very easy" compared to 79% of Non-Hispanic patients. Just over half (53%) of Asian patients felt taking their medication was "very easy" compared to 78% of White and 74% of African American/Black patients. Both Hispanic and Asian populations experienced a harder time understanding instructions and were also less satisfied with answers to investigational medication-related questions from site staff.

The "so what?"

While the method of investigational medicine administration may be challenging and time-consuming to modify, simply providing easy to understand and culturally appropriate investigational medication education and support—particularly to those targeted populations discussed—can readily improve patient experiences and improve compliance. Furthermore, text messaging and other new technologies can also be leveraged to better engage with patients and remind them to take their investigational medicines.

—CISCRP Research Services: Jasmine Benger, Nova Getz, Annick Anderson

CLINICAL OUTSOURCING

CROs TO SEE 12% YEARLY GROWTH TO 2021

The global market for clinical trial services to biopharmaceutical and medical device companies is forecast to grow at 12% year-on-year to 2021, a report from The Business Research Company shows. That is an acceleration from its rate of 10% up to 2017, which raised its value to $44.4 billion.

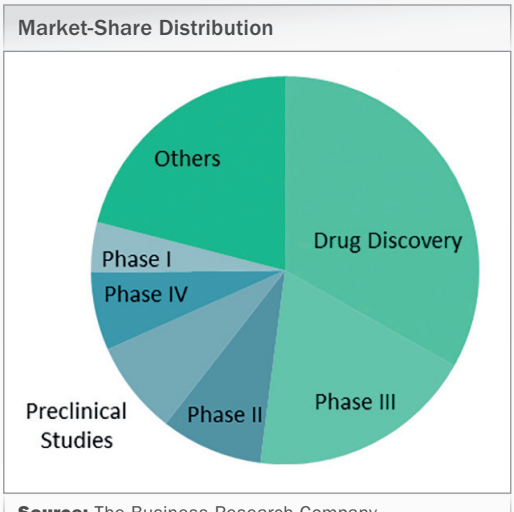
Contract research organizations (CROs) are defined as service providers that offer solutions for the conduct of clinical trials, including initial drug discovery solutions, toxicology studies, bioanalytical services, central laboratory functions, site monitoring, data management services, vigilance, biostatistics, study and development program design and consulting, regulatory affairs, and a variety of post-marketing surveillance services.

By service type, drug discovery was the largest segment in 2017, accounting for about 33% of the CRO market (see chart). By therapeutic area, oncology was the largest segment, accounting for about 25% of the total.

North America is the largest region for the production of CRO services, $18.8 billion, while CRO consumption in North America is worth $20.8 billion or about 47% of the global total. The large market size can be attributed to the presence of a large number of pharmaceutical companies and extensive drug development activity in the region, especially in the U.S. The production/consumption difference is due to the use of lower-cost offshore locations for some CRO activities by U.S. pharmaceutical firms, although the majority of U.S. outsourced activity remains within the country.

Declining growth in the pharmaceutical market is affecting the CRO industry, though not in the obvious way. Recently, the double-digit growth rates of pharmaceutical and biotechnology companies have been shrinking to single digits. Pharma and biotech companies have been confronted with the need to minimize their drug production and development costs. This has forced most of them to evaluate cost-saving options such as outsourcing. Several companies in this sector have already adopted this strategy and outsourced their processes to specialist service providers such as CROs.

IQVIA is the largest player in the global CRO market with a 12.4% share, followed by Laboratory Corporation of America Holdings, ICON Plc, PAREXEL, and PPD.



Source: The Business Research Company

Contract research services market segment shares percentages.

Metabolic disease segment on rise

The largest segment of the $44 billion contract research market is for clinical studies to develop therapies for cancer, but the smaller metabolic disease segment is growing much faster, the Business Research Company report shows.

— Staff Report

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

DRUG ACCESS

EUROPE BOLSTERS COALITION TACKLING NOVEL DRUG PRICING

The late-June announcement that Ireland is joining the Beneluxa initiative on pharmaceutical policy might suggest renewed vigor for the drive to equip national governments with more clout in their pricing negotiations with international drug firms.

The Irish Minister for Health, Simon Harris, signed an agreement on June 22 with his counterparts from Belgium, The Netherlands, Luxembourg, and Austria, the current members of this collaborative alliance, set up with the aim of gaining strength in numbers to tackle the demands of pharmaceutical firms when setting prices, particularly for innovative medicines.

Beneluxa sprang from a widespread sense of weakness among health authorities in Europe, crystallized in 2014 when the hepatitis C drug Sovaldi presented them with the epitome of what had been a growing challenge. A steady flow of higher-priced innovative medicines for relatively rare conditions were becoming a chronic headache for managers of health budgets; but the headache became acute with the sudden appearance of a treatment that was demonstratively effective for a huge population and carried a massive price.

Since the five-member coalition formed, analogous ventures have emerged. In 2017, Cyprus, Greece, Italy, Malta, Portugal, and Spain signed the Valletta Declaration, a similar but still more limited form of cooperation. Bulgaria and Romania head up another group which is trying to extend its cooperation into other Balkan countries.

However, the results so far have been meager in terms of constraining drug prices—and the plea that Belgian minister Maggie De Block issued at the signing ceremony was more an indication of weakness than of strength: "I hope that other European countries will join us soon," she said, "because the more patients we represent, the more our voice will be heard when discussing high-cost innovative medicines."

Even more revealingly, the attitude adopted by the drug industry is as much one of welcome as of fear in the face of this circling of the wagons by health authorities. Research-based companies see that the sort of discussions that take place within these cooperative ventures can play in their favor, by raising the level of debate, by focusing on value rather than merely price, and even by leading to improvements in the speed or efficiency of reimbursement proceedings in some countries. When Ireland signed up to Beneluxa, the Irish Pharmaceutical Healthcare Association immediately saw the move as a potential lever for easing what it depicted as the logjam in Irish regulatory activity.

Criticizing the "slow and inefficient medicines approvals process for Irish patients," IPHA claimed that "Ireland lags the countries in the Beneluxa group when it comes to access to innovative medicines." Ireland is the slowest in western Europe on the availability of new medicines, said Oliver O'Connor, IPHA's chief executive, and it needs to make up lost ground.

"Industry and government share a goal to deliver better access to innovative medicines for Irish patients. It is worth weighing any moves, including Beneluxa, that can help deliver sustained improvements on the availability of new medicines for patients in Ireland," he said.

Perhaps this slow and diffuse building of coalitions across Europe is more appropriately seen not as a combat between governments and drug firms, but as an ill-defined pathway that could lead to better understanding between all the protagonists as the quality of discussions rises. As Beneluxa points out, its cooperation is not limited to joint pricing negotiations. It also works on horizon scanning, on joint health technology assessments, and on data sharing and policy formation. The likelihood is that better-informed health authorities will be better equipped to confront drug firms. Similarly, drug firms will be obliged to present more cogent justifications for their pricing ambitions—but will at least be able to expect a more sophisticated response from authorities. Ultimately, both sides could gain—and the real winners could be patients.

— Peter O'Donnell

NEWS NOTES

SURVEY: MAJORITY OF LEADERS TAKING ACTION TO UNIFY CLINICAL PROCESSES

The latest findings of the Veeva 2018 Unified Clinical Operations Survey revealed that nearly all clinical leaders surveyed (99%) cite the need to unify their clinical environment. Most (87%) report their organizations are taking action with initiatives planned or underway to unify their clinical operations for improved trial performance.

Many have also made progress modernizing their clinical processes with the adoption of purpose-built applications in key areas. Most notably, the number of organizations that have adopted electronic trial master (eTMF) applications has quadrupled since 2014, and a majority of respondents (83%) say they have, or plan to have, programs to improve study start-up processes.

Synteract acquires dermatology CRO

Full-service CRO Synteract recently acquired Cu-Tech, LLC, a dermatology specialist CRO. In coming together with Cu-Tech, Synteract has created a dedicated center of dermatology development, making the combined company the leading midsized global CRO for dermatology clinical trials. Cu-Tech is based in New Jersey.

GSK teams up with 23andMe

In late July, GlaxoSmithKline and DNA testing company 23andMe unveiled an exclusive four-year collaboration that will focus on R&D of new medicines and potential cures, using human genetics as the basis for discovery. The collaboration will combine 23andMe's large-scale genetic resources and advanced data science skills, with the scientific and medical knowledge and commercialization expertise of GSK. The goal is to gather insights and discover novel drug targets driving disease progression and develop therapies based on those discoveries.

— Staff and wire reports

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"Filling the Gaps in Site Selection," Industry statistics show that we continue to rely on the same investigators over and over, regardless of prior performance. This leads to investigator exhaustion, timeline extension and lost opportunity. This co-presentation from IQVIA CTOS and Informa Pharma Intelligence's Citeline, will highlight a collaboration aimed at delivering a unique combination of data, technology and analytics to optimize the site feasibility process. This joint effort offers 'one-stop site shopping' within placement areas ripe for recruitment success.

Learn how the process of site selection for clinical trials can be effectively improved and optimized.

Key take-aways:

"Filling the Gaps in Site Selection" showcases how technology, data and analytics can drive balance in site selection decisions between known and unknown sites with significant performance improvement.

- Eliminate investigator exhaustion
- Expand investigator networks with evidence
- Leverage analytics to create predictive performance indicators

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

Clinical Trials Don't Have to Cost Too Much or Take Too Long

Stephen Arlington, PhD, Paul Chew, MD, Annalisa Jenkins, MBBS, FRCP, Gen Li, PhD

Analyzing data to reveal site performance patterns for better trial planning and execution.

TRIAL DESIGN

The pharmaceutical research landscape is littered with the remains of failed clinical trials. Since 2008, 17.2% of Phase II trials and 12.2% of Phase III studies have been prematurely terminated, according to an analysis of the Phesi database, which comprises more than 320,000 clinical trials and over 500,000 investigators across several hundred disease indications. Given that estimated global pharmaceutical R&D spending currently amounts to $125 billion-$160 billion annually,[1,2] those terminations mean roughly $20 billion of that spending is essentially wasted every year. More importantly, terminated trials dash the hopes of patients who could have potentially benefitted from the medical innovations that might have emerged from successful studies.

The Phesi database reveals that patient recruitment difficulties are responsible for 57% of failed Phase II trials and 54% of failed Phase III trials. Such difficulties result from a variety of factors, including suboptimal protocol design, inefficient business processes (especially with regard to site activation), and poor investigator site performance. These difficulties are avoidable and can be addressed through better understanding of the operational characteristics of clinical trials, which itself can lead to improved clinical trial planning.

The perils of inadequate planning

At the risk of oversimplification, a clinical trial collects and analyzes safety and/or efficacy data from a well-defined group of patients in a highly regulated and carefully controlled setting. Depending on how one defines a variable, it may take several dozens or even hundreds of variables to determine the outcomes of a clinical trial. However, even when a trial sponsor, or the contract research organization (CRO) it works with, does a hundred things right, one mistake can jeopardize a trial's success.

Oftentimes, success may hinge on the trial planner's appreciation of the complexity of the disease, or on a team's ability to determine the appropriate number of patients, the right number of investigator sites, and the optimal duration of the trial. While each of these factors is a major driver of clinical trial costs, the numbers of patients and sites typically generate relatively little discussion from

The Linear Lens

	PHASE II -- ACTUAL	PHASE III -- PLANNED	PHASE III -- ACTUAL
Patients	160	970	970
Sites	48	280	258
Enrollment cycle time (ECT) (months)	14	12	24
Gross site enrollment rate (GSER) (patients/site/month)	0.29	0.29	0.15
Site effectiveness index (SEI)	0.68	unknown	0.71

Source: Arlington et al.

Table 1. An example of a planned versus actual patient enrollment metrics for a Phase III oncology trial.

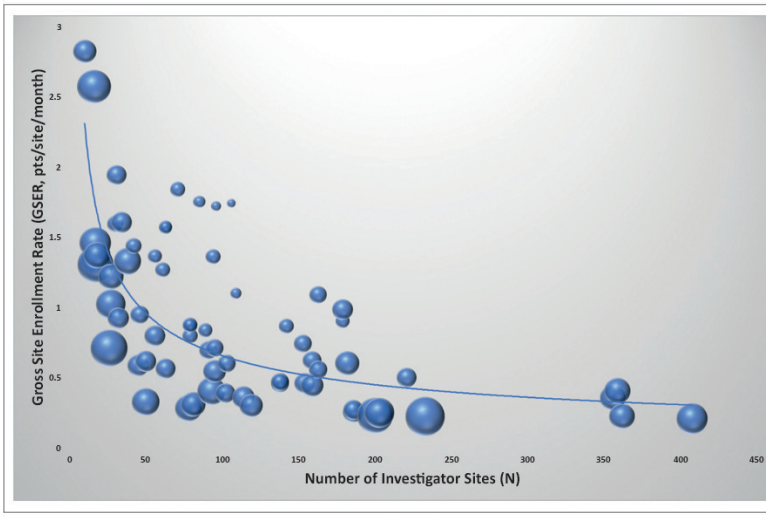
a financial perspective. Moreover, the clinical trial process is idiosyncratic, dependent on variable experience, and usually conducted without regard to the broader experience of similar trials that have already taken place.

To a great extent, the inattention given to these factors stems from simplistic, perhaps wishful planning and unrealistic, uncalibrated expectations: pharmaceutical companies generally want to get their new medicines to patients as soon as possible, at the lowest possible cost.

The desire for speed can encourage a risky form of linear thinking: for many, in a Phase III trial, the operational model is derived from a successful Phase II trial, from which the number of investigator sites is extrapolated in order to attain a similar enrollment cycle time (ECT), which is the elapsed time from first to last enrolled patient, as shown in Table 1 on facing page, a hypothetical example of a clinical program for an investigational anticancer agent.

In Table 1, the trial planners used an assumed linear relationship between number of patients, number of sites, and ECT to extrapolate the Phase II ECT of 14 months to a forecasted ECT of 12 months for the Phase III study. Unfortunately, such a linear relationship does not exist: the actual Phase III ECT was 24 months—twice the forecast. A Phase III trial is not just a bigger Phase II trial; oftentimes, this is a costly lesson.

Volume vs. Performance



Source: Arlington et al.

Figure 1. Number of investigator sites (N) vs. gross site enrollment rate (GSER).

The power of predictive analytics

Phesi has developed a predictive analytics platform that consolidates comparable trial and site metrics to support trial design, protocol design, site selection, and trial execution. Although no two trials are exactly alike, the platform yields a mathematical relationship that enables a "comparison of the incomparables," using the following metrics:[3-5]

- **Site Activation Curve:** The number of sites activated over time.
- **Site Effectiveness Index (SEI):** The area under the site activation curve—a relative measure of the available site capacity that is being utilized over time. The SEI can be measured as the percentage of selected sites open for enrollment over the duration of the enrollment cycle time, or as the percentage of time a single site is open for enrollment compared to the overall trial enrollment duration. As a percentage, SEI is always larger than zero and less than one.[4]
- **Enrollment Curve:** The number of patients enrolled over time.
- **Gross Site Enrollment Rate (GSER):** The effective trial-level enrollment rate, expressed as patients/site/month.
- **Adjusted Site Enrollment Rate (ASER):** The product of SEI multiplied by GSER (SEI x GSER = ASER).
- **Enrollment Cycle Time (ECT):** The elapsed time (in months) from first enrolled patient to last enrolled patient.

Using these metrics, one can reliably analyze data from comparable trials (actuals) and a client's trial (forecast) to reveal patterns behind the numbers. For an extensively studied disease indication, we select a set of randomized clinical trials that are similar to the client's planned trial in terms of number of patients, number of investigator sites, inclusion/exclusion criteria, and other relevant parameters. We then use those parameters to develop a bubble chart that incorporates three variables: number of activated sites (N), GSER, and ECT, where each bubble represents one selected clinical trial. The size of each bubble reflects the length of ECT, with larger bubbles representing a longer ECT.

A sample bubble chart appears in Figure 1, which shows how adding sites to a trial can suppress individual site performance.

It seems intuitive to add sites to a trial in order to have them contribute more patients and thereby reduce ECT. What is less intuitive, however, is that the incremental benefit vanishes at a certain point, beyond which the ECT is prolonged. As Figure 1 illustrates, the declining GSER means each site contributes fewer patients over a defined period of time (ECT). In other words, the point of diminishing returns is reached early in the course of the trial, in part because of slow site activation (a particularly thorny problem for large studies with many sites), and in part because the best sites are recruited first. Late activation of a poorly performing site pulls down the site activation curve. This distinctive pattern holds true for over 1,000 different disease indications we have analyzed, and we suspect it is nearly universal.

Figure 2 (see page 14) further pinpoints the optimized scenario at the point where activating 79 sites would yield an ECT of 273 days. Beyond this boundary, the benefits diminish.

As shown in Figure 2, the enrollment and site activation patterns, coupled with the observed mathematical relationships, essentially enable us to objectively determine the optimal number of sites.

Moreover, the predictive analytics platform facilitates clinical trial design optimization and country-to-country comparison of site performance, among many other possibilities.

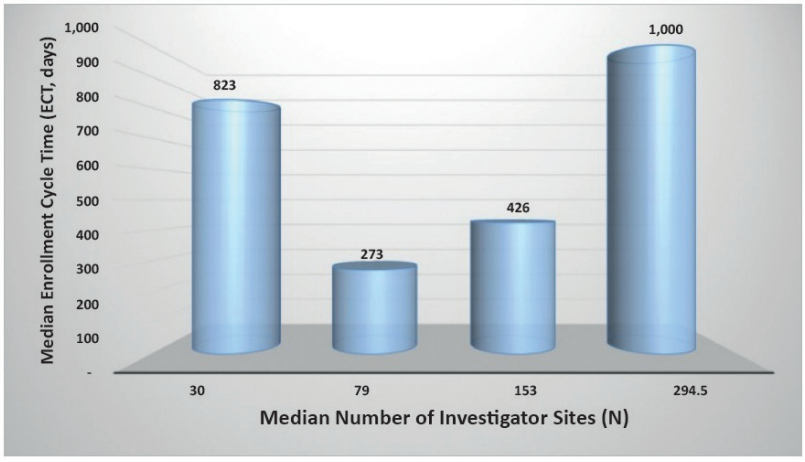
Too many sites

One might argue that even if the GSER decreased, there would still be a surplus of eligible patients to potentially reduce the ECT. But that is not what we get in reality (see Figure 3).

Why do the benefits fall off so dramatically? It's because activating an excessive number of investigator sites yields a larger trunk of non-performing sites that drain financial resources and, in all likelihood, prolong the ECT. In the example illustrated in Figure 3, a total of 227 sites were activated in this trial, but only about 140 sites contributed patients. Moreover, the 77 sites activated in the last six months of the trial did not contribute a meaningful number of patients. The number of activated sites far exceeded the 120 sites recommended via our optimization analysis, as illustrated in Figures 1 and 2. Additionally, the 87 non-performing sites created a financial exposure amounting to $10.4 million, based on an assumed $30,000 in site activation costs and $3,000 per site per month over a 30-month duration. Those costs yielded an SEI of 44%, significantly lower than the recommended 60% SEI value for this trial.[6]

The disparity between actual and recommended SEI illustrates one of the perils of activating too many investigator sites: activating a large number of sites takes time, especially in the early stages of a trial. In the trial described above, the team was forced to push too many sites forward with limited resources, and a large percentage of sites were activated near the end of the ECT, when the team was spread too thin by focusing on too many non-productive tasks, and was unable to focus on maximizing returns from the most productive sites. In short, there is such a thing as "too big to succeed."

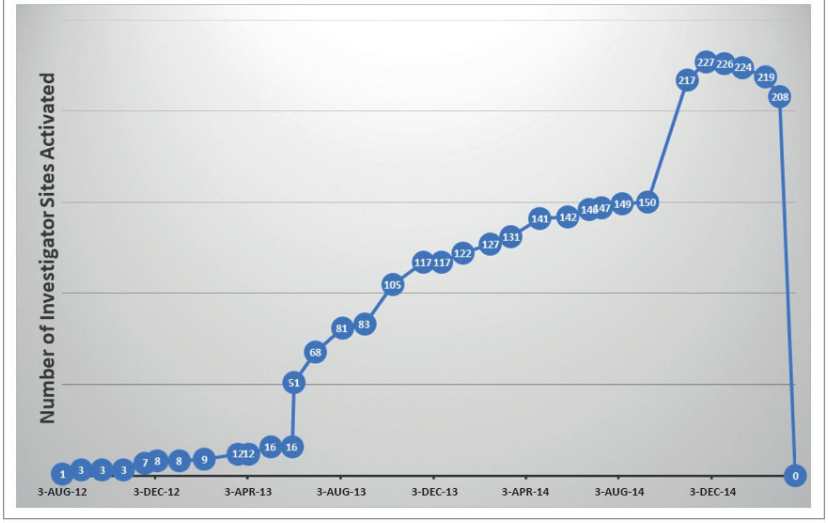
Search for Sweet Spot



Source: Arlington et al.

Figure 2. The "sweet spot" that optimizes enrollment cycle time and investigator sites (N).

When More is Less



Source: Arlington et al.

Figure 3. "Too much, too late": larger number of sites added too late to contribute meaningful numbers of patients.

Too few sites

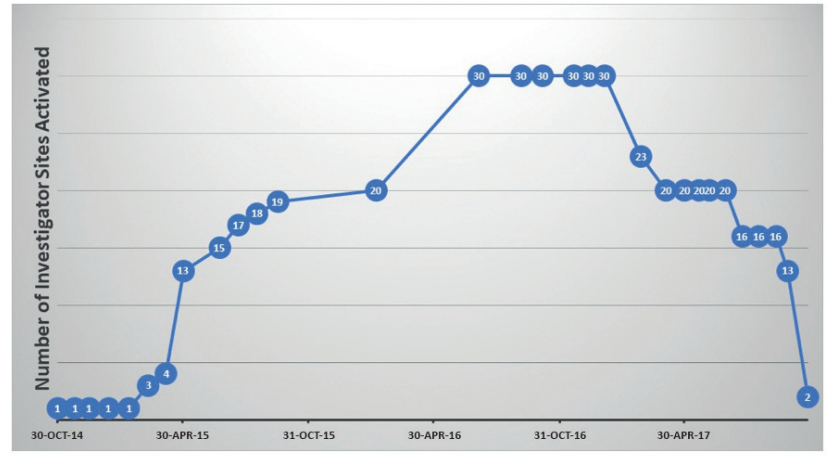
Moving in the opposite direction risks crossing another boundary, one that results from activating too few sites rather than too many. Such a situation may occur when a budget-conscious sponsor funds an insufficient number of sites (see Figure 4 on page 15).

In this case, analysis of our database yielded a recommendation of 80 sites and a forecasted ECT of 15 months. The trial team, restricted by available funding, decided to activate 30 sites instead. The lower number of sites reduced site activation costs by about $1.5 million. The trial team used these savings to extend site management over a much longer time frame, from 15 months to 35 months. Unfortunately, the savings were negated by extra costs for drug supply, medical monitoring, and various other project management costs. The 20 extra months in ECT, therefore, constituted wasted time and a lost opportunity to optimize the site activation timeline. Presumably, advance knowledge of these opportunity costs would have prompted management to make a different decision about this trial.

Enhancing organizational awareness of the boundary

The beauty of the analytics platform is that it is objective and quantitative, enabling trial planning and execution in an integrated fashion. Nevertheless, true integration is not a given. In many big pharma companies, and even in some small ones, siloed decision-makers can jeopardize clinical trial success. Even if the trial planner is aware of the point of diminishing returns (and of the risks of disregarding this critical juncture), this knowledge is irrelevant unless it is shared across the organization. That speaks to the importance of cross-functional communication between the medical, clinical, commercial, regulatory, and finance teams—as well as between sponsor and CRO—to optimize decision-making. When each of these parties understands the importance of the factors that affect site activation and patient enrollment, and of the variables that determine enrollment rates and site performance, the organization as a whole (and its CRO partner) can successfully navigate what might otherwise be a perilous clinical trial landscape.

When Less is too Little



Source: Arlington et al.

Figure 4. Investigator site activation: too few sites.

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Blockchain in Clinical Trials—the Ultimate Data Notary

Artem Andrianov, PhD, Boris Kaganov, PhD

Assessing the benefits of using blockchain technology as a notary service in the network sharing of clinical data.

SUPPLY CHAIN

Blockchain technology may the biggest achievement of cryptography of the last decade—and there are few industries craving its core ability to provide guarantees about data safety and authenticity as much as the clinical trials enterprise. Source data verification (SDV), which today often accounts for 20%–30% of the clinical trial budget, becomes unnecessary when blockchain disrupts pharma.

However, let's start from the very beginning of that story. Hashing is the cornerstone technology of the blockchain. The algorithm takes a stride of arbitrary data of any size and produces a "hash," which is a big number from a selected range with two main properties:

a) It is very unlikely that different data would have the same hash.

b) That calculation is reproducible by anyone knowing the algorithm.

The blockchain is used for storing hashes of a combination of important data with an exact time of saving (timestamp). It can then be used as evidence that the data existed at a certain moment and was not forged or altered.

These evidences cannot be erased because the blockchain protects them. That allows their use in clinical trials by keeping track of every step and saving a timestamp; e.g., when source data is entered at a clinical site and transferred into the electronic data capturing system of a clinical trial, there is no need to check the correctness of the transfer anymore. Blockchain does it for us.

For pharma, it is vital to make clinical trials more reproducible, ensuring data for each step is not falsified. For that, every document prepared before a start of a study (informed consent, study protocol, study plans, regulatory documents, etc.) should be timestamped to create a proof that it existed in that exact form before the start of the trial. It is especially important for preplanned endpoints. In addition, when the study starts, ongoing reports are treated the same (i.e., monitoring visit reports). Each measurement in a trial can be notarized to be safe from forgery and corrections that violate a protocol, good clinical practice (GCP), or even the law. This technology would increase the credibility of clinical trial results. The notarized data exists outside of the blockchain boundary in safe storage and only digital thumbprints of it are inside. Such a permanent catalog of documents significantly reduces the costs for audits, file reviews, lost documents, post-closing, and litigation. Blockchain can also help with pharmaceutical supply chain management, tracking drugs for better accountability and the supply chain integrity.

Thus, blockchain is used as a notary service and has the potential to reduce systemic risk, increase data quality, and decrease risk of fraud by a notarized process because of the programs open and decentralized nature.

Data safety guarantees

What does it mean that a blockchain is decentralized? It is a network (so-called peer-to-peer), where data is broadcasted by one peer and received by another, which confirms that fact by broadcasting a hash of the data. Then the hash is received by a third peer and it treats the hash itself as the data and then issues the hash of the hash, etc., effectively forming a chain of hashes. However, each of the peers, before hashing, can combine the received data with other information (timestamp, data from third parties) and that combination is named a "block." It happens because computing a hash is computationally costly; it is cheaper to compute a hash for a larger bunch of data. A chain of hashes can be looked

at as a chain of hashed blocks—which is why it is called blockchain. That chain is kept in a distributed database called a ledger, which is a permanent memory of all peers.

In a classic blockchain (e.g., Bitcoin), computational costs are intentionally high and even increasing by design if the number of peers grows. In that way, the blockchain controls the creation of new blocks, making it impossible to tamper with the system and trick other users by lying about a true value of the existing block. To do that, an attacker needs to outperform in computing power all peers who produced that block and every block in a chain after it. That algorithm is named proof-of-work (because a new block existence proves that a significant work was done to produce it) and it is a "consensus algorithm" in the sense that it allows reaching agreement about recognizing new blocks.

As a result, immutability of data is guaranteed by computing power or hundreds of megawatts of energy spent by miners of new blocks. In other approaches, guarantee is an amount of memory or disk space. So such systems are most credible in terms of data authenticity, especially Bitcoin.

The other side of the equation is that you cannot send data to such a blockchain for free. Any transaction costs money, so in practice, for example, electronic signature services using Bitcoin blockchain for notarizing document signatures accumulate many signatures and send them in large bunchs or otherwise pay a fee for sending each signature as a transaction. In the first case, the wait is hours for finalizing a signature; in the second, it's tens of minutes.

These fees occur because the blockchain is paired with cryptocurrency. It is needed to reward system participants, do that proportionally to contribution of their power, and allow to exchange that reward for real money. Actually, a peer needs to pay because they are not trusted by other peers because of his or her anonymity.

Public and private blockchains

To that point, we were discussing public blockchains, where anybody can anonymously become a member of the system. The pricing component gives unparalleled confidence that the data was not manipulated. nevertheless, this confidence is limited, too, because any blockchain is not as decentralized as it is claimed. They have an unspoken dependency on developers, which can change system rules whether by releasing a new version of a software commonly used for a blockchain or even sometimes directly. This is often an open source code, but, in practice, users understand that without a skillful team, the system quickly becomes outdated, which is why the developer's authority is weighed so much. At times, unhappy users refuse to follow, and blockchain splits. Such an event is referred to as a "hard fork." These can become a threat if researchers want to conduct a study lasting several years, because during a longer period, the study data may unwillingly face an urge to select a partition to follow.

However, there are also private blockchains without transaction costs and such a dependency on third parties. In addition, currently, a key question about applying blockchain to clinical trials is whether to use a private or a public blockchain.

In a private, or "permissioned," blockchain, there is an administration controlling membership. It is important because it controls membership of participants validating transactions. A permissioned blockchain cannot guarantee data immutability because controlling authority can become flawed by an attacker, then establish a coup of flawed validators and then cancel or create arbitrary transactions. Due to regulatory pressure, even if a private blockchain is semi-decentralized, it is impossible to build a censorship-resistant system on the base of it.

A permissioned blockchain cannot guarantee data immutability because controlling authority can become flawed by an attacker, then establish a coup of flawed validators, and then cancel or create arbitrary transactions.

Data manipulation becomes even easier as long as private blockchains do not use proof-of-work consensus. It is impractical because it cannot be expected that third parties not controlling blockchains such as administration (and, thus, trusting it less than public blockchains) would spend their computing power on a big scale for verifying transactions. As for internal resources belonging to the administration, they do not spend their computing power. In these cases, the system may lose the competition to other private blockchains that are more cost-effective. Instead, private blockchains use proof-of-stake or consortium consensus algorithms.

In proof-of-stake, a new block is proven if a producer has a certain amount of cryptocurrency. So less work is needed for a proof and as a result, transactions happen much faster. You do not need to wait for hours until the blockchain approves a transaction by a new block; it is ready in seconds. That is critical if one is waiting for a sign-off of a regulatory document in a clinical trial that has many signatures and needs to immediately make sure all signatures are stored safely in the blockchain. The industry has a large population of trial participants that will need to have their data validated in a timely manner, so both a quick consensus algorithm and a large number of peers in a blockchain are necessary.

There is an ongoing debate on how to organize that network. One of the most probable ways is the consortium or Byzantine consensus algorithm that implies peers know each other in advance, and when a new block is produced, they vote for it and are able to establish consensus based on recognized votes of others. This approach involves significant trust in participants and it is natural for associations consisting of well-known and authoritative health organizations. If a private blockchain is controlled by a consortium of organizations, it may be the best fit for clinical trials, if controlling parties include authoritative medical institutions. A legal authority

potentially would take part, too. For example, FDA is currently conducting research in that direction with IBM.

Global network of medical records

It is difficult to overestimate the potential positive impact of such a network allowing the transparent sharing of clinical data between all industry stakeholders. It is anticipated by many that the system would finally become a common industry electronic health record (EHR) format, which the sector needs because one of the biggest problems is the lack of visibility. It will increase transparency and cross-institutional visibility of the process of unfinished trials because it will be much easier to share information that is not confidential (for example, the overall number of participants), especially with smart contracts which are discussed ahead. Recent attempts to build a prototype of such a network are MedRec and Gem Health blockchain initiatives.

Being a consortium blockchain, the network can still avoid complete dependence on a particular blockchain implementation or community. It is possible to have the best of both worlds by using private consortium blockchain as an agile instrument for ongoing operations but, in addition, leisurely send data for storing it in a public blockchain to produce better guarantees. Most advanced digital asset management solutions are saving hashes of the same data in several blockchains at a time, achieving multiplication of safety guarantees.

> With blockchain, each medication prescription is like a deposit, and when a doctor discontinues a drug, it is a withdrawal.

Of course, a potential EHR system is not limited to clinical trials. The most important use of it is a media for sharing medical information, health data banks, and research commons, while keeping information about patients and making it available securely for authorized doctors and clinical researchers. With blockchain, each medication prescription is like a deposit, and when a doctor discontinues a treatment, it is a withdrawal. So it is possible for another doctor to see the balance without looking through every deposit operation. Also important for patient privacy is that institutions will not need to send data back and forth; they just use the common ledger. Hence, blockchain increases confidence in patient privacy.

That system enables organizations to better coordinate compliance or any type of audits, across multiple sources, ensuring a fully complete file every time. Additionally, the global medical records network can support a registry of medical devices being a basement for Internet of Medical Things (IoMT).

The blockchain can help decentralize clinical studies because of its own decentralized nature. Currently, clinical trials depend on having consistent reporting locations to ensure proper collection of data. But it can be problematic in terms of retention because they are not likely to be convenient for every patient. As the level of inconvenience increases, the odds of a trial completion fall. But blockchain technology allows clinical trials to be monitored from a wider variety of locations, use a wider base of staf,f and have higher patient privacy and information security at the same time, thereby increasing completion rates.

Smart contracts help with privacy and automation

There are different approaches to address the need for privacy in clinical research. Enigma project (under construction) is a public computation blockchain platform that allows privacy to be kept about data by sending bits of it to some random subset of the system instead of to every participant, like other public blockchains do. Therefore, the full case data is never disclosed. When implemented, it will allow, for example, scanning of genomic databases for candidates taking part in clinical trials, simplifying the process tremendously.

That scan will be done by smart contracts, the programs starting to work fully inside blockchain automatically when some event happens in it. A smart contract can only be fulfilled or canceled; it is impossible to hang in the middle of a contract. They provide failover because computations can be executed on any machine and are started again if a machine fails. It is similar to a cloud service but not bound to a datacenter. Though authorization and identity remain open issues for smart contracts executed on blockchain-enabled networks, there is promising ongoing work. Many use cases mentioned above can be improved by moving validation logic inside a blockchain as smart contracts. Smart contracts make possible complete automation of some operations, for example, to enroll a patient completely automatically, if a contract gets evidence of consent. It may be a digital thumbprint of a consent form automatically sent to blockchain by a interactive voice/web response system (IWRS) web server. In the health records (EHR) network, informed consent can exist as a form of broader concept—a permission given by a patient and implemented as a smart contract for certain actions with his or her private medical data. These permissions can be fine-grained and allow reading or writing a certain part of a patient's data.

It is also possible to conduct much more complex preparations for a clinical trial, for example, transparently pairing donors of organs easier and more reliably than current methods. From a patient viewpoint, using this technology would make it easy to know exactly where you stand in line—and trust that you will stay there. That is why these systems could help drive collaboration between participants and researchers around medical innovation, for example, in population health management.

The smart contract can also be very useful at the step of closing a clinical trial database, doing that automatically when conditions are met. Some outcomes can be calculated and reported completely automatically. Regulators and contract research organizations (CROs) can have their own contracts automating what is possible to automate and make their work easier. Smart contracts are not legal contracts but can be used for validation of them, effectively replacing an arbiter or custody. They are also useful for claims adjudication and billing management, economizing money by eliminating the need for intermediaries and cutting administrative

costs. It is known that 50% of clinical trials go unreported and often fail to share study results. Blockchain with smart contracts can significantly improve that situation and address the issues of outcome switching and selective reporting.

Procuring clinical data privacy with blockchain storage

We already discussed a case of storing trial data out of blockchain (the so-called off-chain solution), but it is also possible to protect confidential clinical trial data by using a distributed storage on top of a blockchain. It avoids having two sets of permissions—one for reading off-chain data and another for conducting operations committing to the blockchain, thus simplifying the process and making it more secure. Pieces of kept data are encrypted and distributed between blockchain peers and no one besides the owner can decrypt it. In this case, they are file servers competing in a storage marketplace for storage users' money. So as an alternative to cloud storage, it claims better privacy and even better benefit-cost ratio. That approach also facilitates decentralized clinical research projects that can query big data in a scalable manner.

Also in the area of big data, a perspective use of blockchain for clinical trials is genomic data management. In this approach, versioning of documents is not something external to the blockchain; so not only is each version notarized, it is also a succession of versions.

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To Sign or Not to Sign FDA Form 1572?

Natalia Buchneva

Exploring that pivotal question for clinical investigators, sponsors, and global CROs.

PEER REVIEW

An ever-changing regulatory framework is the biggest challenge for multinational clinical trials today. Back in 2009, the clinical research world welcomed the launch of the European Medicines Agency (EMA) and FDA good clinical practice (GCP) initiative that set the goal "to increase globalization of clinical trials" and improve cooperation with the non-EU regulatory bodies to standardize GCP interpretation globally.[1]

Clinical Trial Regulation No 536/2014 was developed in 2014 to consolidate the intent to "harmonize the assessment and supervision processes for clinical trials throughout the EU" and to streamline the application and approval processes for market authorization when the clinical study is conducted in several EU countries.[2]

In the meantime, some European countries considered whether to reinforce the local expectations for the conduct and reporting of clinical trials on their territory, while awaiting the implementation of the Clinical Trial Regulation No 536/2014.

In January 2018, the German Federal Authority for Health Protection in relation to Medicinal Products and Medical Devices (Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten, further referred to as "ZLG") published Vote summary V05005 "Handling of FDA 1572 form in Germany."[3] This local guidance attracted major reaction in the clinical research professional media, as it is being interpreted in conjunction with the recommendations from the Danish Medicinal Agency (Laekemiddelstyrelsen, further referred to as "DMA") on the use of the FDA 1572 form released in October 2017 in Denmark (see Table 2 on page 22).[3,4]

There have been prior occasions when non-U.S. clinical investigators refused to sign the FDA 1572 form. However, these cases were individual investigators' decisions, rather than representing the point of view of the country or region. There has previously been no alternative non-U.S. regulator´s statement available; therefore, the instructions on the FDA 1572 form itself and the recommendation from the *FDA Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions: (Form 1572)* of May 2010 were, in general, followed by sponsors of clinical trials and the involved investigators.[5]

FDA expectations

The FDA 1572 form is one of the key documents within the investigational new drug (IND) submission to the agency in support of marketing approval. It is treated by FDA as "an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with the FDA regulations related to the conduct of clinical investigations."[5]

By signing this "statement," the investigator indeed pledges to adhere to the following regulations under Title 21 "Foods and Drugs" of the U.S. Code of Federal Regulations (CFR) related to the conduct of a clinical trial:

- Title 21 CFR Part 50 (obtaining informed consent)
- Title 21 CFR Part 56 (ensuring that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for review and approval)
- Title 21 Part 312 (compliance with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements)
- Title 21 CFR 312.62 (maintaining adequate and accurate records, making these records available for inspections in accordance with 21 CFR 312.68)
- Title 21 CFR 312.64 (reporting of adverse experiences that occur in the course of the clinical trial)[6]

As the standard for the conduct of clinical trials in the U.S.

and EU is similar, sponsors of clinical studies were submitting the non-U.S. investigators as IND sites and were collecting FDA 1572 form as part of the application.

The legally binding nature of the signed FDA 1572 form is underlined on the form itself stating that "willfully false information is considered criminal offense U.S.C. Title 18, Sec. 1001." However, this is being questioned by the Danish and German regulators, and they promote the introduction of standpoints of non-U.S. regulators to address compliance with local laws, Clinical Trial Regulation No 536/2014, and CFR Part 21.[6]

Applicability

The following scenarios are mapped out for sponsors carrying out multinational clinical trials with U.S. and non-U.S. sites, or solely non-U.S. sites as per *FDA Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions: (Form 1572)* (refer to Table 1).[5]

Following 21 CFR 312.120, FDA commits to review any foreign study or data that are submitted within marketing authorization application in the U.S.; however, only the GCP-conformant clinical trials where the non-U.S. investigators will agree to allow FDA inspections, if necessary, will be accepted.[7]

Multinational Trials with U.S. and Non-U.S. Sites

SITE LOCATION	IND STUDY	NON-IND STUDY
U.S.	**Title 21 CFR 312, 312.62, 312.64, part 50 and part 56**	N/A
	FDA 1572 form must be collected	N/A
Non-U.S.	**Title 21 CFR 312, 312.62, 312.64, part 50 and part 56** and local legislation for certain non- U.S. countries	Local legislation and **Title 21 CFR 312.120,** only if submission to FDA is planned
	FDA 1572 form must be collected	**FDA 1572** form is not required and should not be collected
	Waivers from Title 21 CFR Parts 50 and/or 56 for every or certain sites under an IND may be granted by FDA	The FDA may agree to **waive** any applicable requirements under Title 21 CFR 312.120 paragraphs (a)(1) and (b)
U.S. + Non-U.S.	**Title 21 CFR 312, 312.62, 312.64, part 50 and part 56** and local legislation for certain non- U.S. countries	Local legislation and Title 21 CFR 312.64 and 312.120
	FDA 1572 form must be collected	**FDA 1572** is required to be signed by the U.S. investigators only
	Waivers from Title 21 CFR Parts 50 and/or 56 for every or certain non-U.S. sites under an IND may be granted by FDA	The FDA may agree to **waive** any applicable requirements under Title 21 CFR 312.120 paragraphs (a)(1) and (b) for every or certain non-U.S. sites

Source: Buchneva

Table 1. FDA guidance scenarios for domestic and foreign studies.

The statistics about the FDA acceptance rate of the data submitted under 21 CFR 312.120 is limited, the FDA guidance (question 14) recommends that "if the sponsor intends to submit the data in an application for marketing approval, we recommend that the sponsor identify the foreign sites that will not be conducted under the IND and discuss plans to pool the data from U.S. and foreign sites with the appropriate FDA review division."

> Time will tell whether Denmark and Germany become trendsetters for other EU countries or if their decision will remain isolated in their view of the FDA 1572 form.

EU country-level decisions

The DMA and ZLG advocate for triggering the option is mentioned in question 10 of the FDA guidance: "If local laws or regulation prohibit the signing of a 1572, FDA would expect the sites to operate as non-IND sites and the study conducted as a non-IND study."[5]

In DMA´s opinion, the Danish investigators must not sign FDA 1572 form, as "a clinical trial conducted at a site in the EU and European Economic Area (EEA) cannot be conducted under any foreign country legislation."4

Vote summary V05005 recommends that the German investigators should preferably be involved as the non-IND sites in the relevant studies. Additionally, the sponsors have the possibility to maintain the German sites as IND sites and collect FDA 1572 forms, provided that certain criteria are met. The details of the DMA´s and ZLG´s recommendations are presented in Table 2.

FDA 1572 form forecasts

Time will tell whether Denmark and Germany become trendsetters for other EU countries or if their decision will remain isolated in their view of the FDA 1572 form. The countries outside of the EU tend to accept FDA requirements to keep the investigators that agree to sign FDA 1572 as the IND sites, though, there is no known official position and isolated refusals from the non-EU investigators cannot be excluded. Of note, the number of other individual EU investigators who are refusing to complete the FDA 1572 form is growing. The investment will most probably be justified proportionately with the amount of data that will be produced by the German and Danish sites in support of the IND application. Sponsors and global CROs are striving to take the burden off of investigators´ shoulders and tend to abandon completion of FDA 1572 forms in

the countries where they are explicitly forbidden and for those investigators who are not comfortable with signing off the forms.

In absence of EMA´s official standpoint, clinical research sponsors operating in Europe are hesitant to revise their overall approach to handling the non-U.S. sites as non-IND sites and abolish collection of FDA 1572 forms in all EU countries.

As part of an associated risk mitigation program, the internal regulatory groups at sponsors and CROs were alerted to monitor the release of other EU and non-EU inspectorates' opinions about the use of the 1572; statistics on acceptance of the foreign data by the FDA are being collected and the EU and non-EU clinical investigators who deny their sites to be maintained under IND are being tracked.

The clinical research world anticipates that revisions and clarification of the local laws in certain EU countries are associated with major regulatory changes in Europe, such as addressing Brexit in 2019 and the recent application of the General Data Privacy Regulation (GDPR) (EU) 2016/679 in May. It is essential, therefore, for the clinical trials market in Europe that Clinical Trial Regulation (EU) No 536/2014 is adopted and the balanced and EMA and FDA mutually recognized improvements are considered.[2,8]

DMA and ZLG Recommendations

	DMA	ZLG
Format	Questions and answers on the official DMA website	Official vote binding on the territory of Germany
Recommendation	Danish investigators must not sign FDA 1572 forms The EU and EEA sites should be included in the same multinational trial and submitted to the FDA as non-IND sites	The sponsor should preferably involve German sites as non-IND sites. However, the sponsor can submit German sites as IND sites if the following criteria are met: - The clinical trial agreement with the PI and/or institution explicitly states prevalence of the EU or national law over U.S. law - A comparative analysis to capture the discrepancies between the legal provisions in Germany/Europe and in the U.S. is ensured - German investigators are trained in CFR requirements Provided the above expectations were met, the FDA 1572 form can be signed
Penalty	No penalty defined	Sponsors will receive major findings if signed 1572 forms are filed at German sites without above requirements being addressed German investigators may receive findings for completing and providing the FDA 1572 form to sponsors, however, the severity of the finding will depend on the circumstances

Source: Buchneva

Table 2. DMA and ZLG´s expectations on handling FDA 1572 form.

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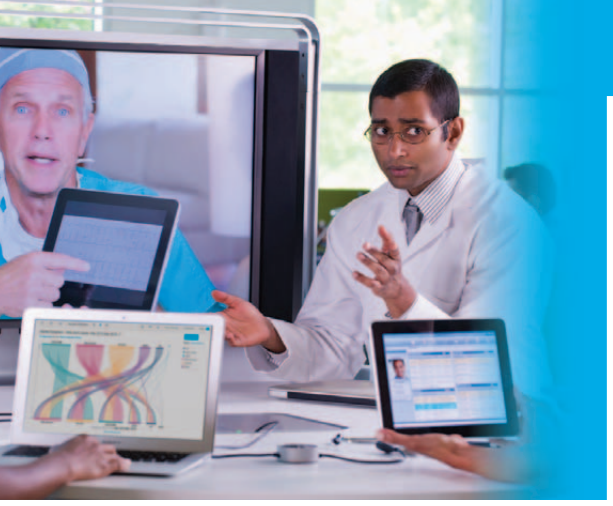

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For technical questions about this webinar,
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Can Sponsors Answer 6 Questions Regulators Ask During Audits?

Switching from paper records to an electronic drug accountability IRT system can benefit sites during FDA trial site audits.

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From 1977—when the FDA began routine clinical trial audits—to 1990, insufficient drug accountability records were found in 25% of audited sites. From 1994 to 2010, FDA investigators found inadequate drug accountability records in about 15% of sites audited in the U.S. and 20% in Europe.

FDA trial site audits are designed to evaluate the conduct of research and ensure patients' rights, safety, and welfare have been protected. During an audit, the FDA investigates six areas to determine whether a site is in compliance with federal drug accountability regulations:

1. Who is authorized to administer or dispense the investigational drug?
2. Has the investigational drug been supplied to any unauthorized person?
3. Can the records for investigational drug inventory be reconciled, i.e., the quantities shipped, received, used, and returned or destroyed?
4. Can drug shipments, dispersals, and returns be verified?
5. Is the drug stored in the manner mandated by the protocol?
6. Does the storage of drugs with the potential of abuse meet the federal regulations for controlled substances?

A failed site audit can lead to costly delays, non-approval of the investigational drug, and/or criminal liability. Sites with inadequate drug accountability management may inadvertently increase safety risks for patients. For example, site staff might disperse the wrong dose or the wrong drug to patients.

Sponsors and contract research organizations (CROs) can prevent problems with paper records and ensure trial sites comply with federal regulations by adding electronic drug accountability to an existing IRT (interactive response technology) system. Electronic drug accountability is proven to increase patients' safety, save time and money, and ensure data validity.

IRT systems have been used on thousands of clinical trials for a myriad of tasks, from patient randomization to drug supply management and allocation. IRT helps enable drug accountability because it tracks drug dispensing units by warehouse, depot, and site location as well as by batch, bulk lot, packaging step, label group, and patient allocation.

All trials can benefit from using IRT for electronic drug accountability management because it's designed with safeguards that reduce the risk of human error. It can automatically timestamp dispensing information; flag entries that do not adhere to protocol; enforce compliance by mandating staff to write summary statements for potential protocol deviations; and, create an audit trail with electronic signatures. IRT also allows for remote, site-level monitoring of drug accountability logs. These capabilities and the built-in safeguards make electronic drug accountability a more accurate and efficient method than paper.

IRT centralizes information and reports it in a uniform format that is always available for review. This is a vitally important feature for trials of drugs with the potential for abuse. For this type of trial, the FDA mandates sponsors provide all information, including case report forms and final outcomes on all instances of drug diversion, discrepancies in inventory of the clinical supplies of the study drug, and noncompliance and protocol violations. Complying with this federal mandate requires a substantial increase in the administrative burden on site staff when paper-based methods are used. The availability of centralized trial information provided by an IRT system is invaluable for this and other tasks, including reconciling inventories of drug supplies at study termination.

Organizations should plan for some resistance to change before undertaking the switch from a paper to electronic drug accountability system. Stakeholders should develop an implementation plan for the change and write standard operating procedures. If done correctly, electronic drug accountability combined with an IRT system will help ensure sponsors and CROs can answer those critical six questions regulators ask during audits.