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Decentralized Trials, Pros and Cons

A s we continue to keep our eye on decen-
tralized trials advances, a recent survey re-
leased by Oracle, and detailed in a recent 
webinar from Applied Clinical Trials (see: https://bit.
lv/3lxhKR4), showed that 76% of 252 industry 
respondents noted that the pandemic sped their 
adoption of decentralized clinical trial methods. 
The most common decentralization steps taken 
were patient-facing technologies or alternatives 
(64%), protocol redesign (63%), and investiga-
tor-facing technologies or alternatives (53%).

However, it is data issues and regulatory con-
cerns that held most back from adopting decen-
tralized trial methods—specifically, ensuring data 
reliability and quality and data collection. Also, 
to wearable and remote monitoring, the respond-
ets’ top concerns are a different approach to re-
view, manage, and interpret data (50%), expense 
(46%), and complicated regulatory considerations 
(41%). Additionally, from the 24% of respondents 
who reported that the pandemic had not acceler-
ated their adoption of decentralized clinical trials, regulatory concerns (42%) were a top reason.

During Informa’s Clinical Trials in Europe 
virtual event, the panel discussion “The Future of 
Clinical Trials” was heavily weighted toward 
the many advances in technology used in clinical 
trials during COVID, and practices such as decen-
tralized trials. Panel members Kenneth Getz, 
Deputy Director and Professor, Tufts Center for 
the Study of Drug Development, Tufts University 
School of Medicine, and Kai Langel, Director, 
Janssen Clinical Innovation, took a moment to 
discuss whether industry will continue with its 
advances post-COVID.

Langel reiterated that as a global experiment, 
aspects brought forward by COVID are work-
ing out and regulators are OK with many of the 
changes, and, therefore, what’s successful will 
remain. He suggested that protocol deviations 
during COVID were not perfect but we can learn 
from that. “There will be data points that worked 
extremely well, and those that will show how they 
could improve,” Langel maintained.

Getz admittedly offered a “somewhat cynical” 
perspective based on historical data. “I think a lot of 
change in behavior in response to the pandemic 
may be more of a short-term or one-time occur-
rence, even though it has facilitated much more 
widely spread use of many approaches supportive of the remote and virtual clinical trial activity,” 
he said.

Based on an audience poll around barriers to 
decentralized trials, Langel expressed surprise 
that no one pointed out costs related to decentral-
tized trials, saying costs will go up. “Home nursing is an expensive service as opposed to asking pa-
ients to travel to site,” he said. “But in many stud-
ies, such as rare diseases, the research gets done 
faster and better, so that trade-off can be worth it.”

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Regulatory Data: How Technology Can Help ClinOps Survive
Joseph Constance

Clinical operations professionals, burdened by lack of data standardization, turn to technology in hopes of streamlining regulatory processes for the future.

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Pandemic Shines Spotlight on Clinical Trial Conduct and Regulation in 2020

The imperative to prevent, treat, and cure the deadly COVID-19 virus altered research and drug development priorities and regulatory oversight this past year as the research community devised new strategies for testing compounds with potential to mitigate the virus’ lethal affects. FDA issued guidance and advice on how sponsors could obtain necessary data through modified research programs, while federal agencies provided billions in financial support to accelerate drug and vaccine development and production.

At the same time, FDA faced challenges to its independence and credibility from often divergent demands from the White House. A central topic was how much clinical data FDA would require to approve Emergency Use Authorization (EUA) of experimental COVID therapies and vaccines. FDA’s fairly new commissioner, Stephen Hahn, a respected oncologist, but with little government experience, became entangled in these issues, raising fears about growing public “vaccine hesitancy” if companies and regulators took shortcuts to speed the development of COVID vaccines.

The debate came to a head in October as vaccine experts from leading medical institutions agreed with FDA staff on the need for sufficient safety and efficacy data prior to authorizing any COVID vaccine for administration to millions of individuals. Manufacturers backed FDA’s demand for two months of safety data following vaccination and at least 30% efficacy in a randomized controlled trial. A main question was the ethics and practical challenges of continuing controlled studies after finding one vaccine safe and effective.

Transparency and innovation

The demand for greater access to information on research initiatives exposed the public to a wide range of usually confidential R&D and analytical information. In August, leading vaccine manufacturers began releasing detailed research protocols for Phase III studies, including enrollment goals for treatment and control arms, dosages, and number of COVID cases in each group needed for interim analysis and data safety monitoring board review.

While shifting many FDA staffers to COV-19 product development and review activities, FDA offices also worked overtime to meet schedules for vetting and approving new drugs and medical products to treat many other medi-
program also calls for federal agencies that fund medical threats. and for responding to future pandemics and bio-
for treating patients in acute care medical facilities listed products are identified as those most needed vaccine delivery (see: https:/ /bit.ly/3mv8b6m). The PPE, monitoring devices, ventilators, and items for nuclear threats. An additional list covers 96 impor-
diments able to protect against emerging infectious active pharmaceutical ingredients (APIs) for treat-
list includes 233 drug and biological products and essential medicines list in 30 days. The resulting bit.ly/37pVL9J) instructing FDA to develop the executive order issued Aug. 6, 2020 (see: https:/ /). The pandemic slowed, but did not derail FDA initiatives designed to improve the regulatory process. The Center for Drug Evaluation and Research finalized the overhaul of its Office of New Drugs to have more review offices and divisions and a team-based, “integrated review” for assessing NDAs. Generic drugs and biosimilars continued to draw attention as important for managing drug shortages and for ensuring consumer access to affordable medicines.

The public debate on vaccine R&D also highlighted the critical role of FDA’s Center for Biologies Evaluation and Research (CBER) and its director Peter Marks, which issued guidance in June clarifying requirements for developing and testing new COVID preventives. In addition, CBER’s Office of Tissues and Advanced Therapies continued to cope with a surge in proposals for developing new cellular and gene therapies, many raising challenging and unique medical and technical issues.

FDA has approved more than 40 innovative medicines this past year and worked hard to meet user fee timeframes for prescription drugs, generics, and biosimilars—vital programs that face revision and renewal in the coming year. At the same time, officials note that researchers designed and launched more than a thousand clinical trials for COVID treatments, but most, unfortunately, appear too small and inadequately structured to yield any useful information. With COVID-19 again surging across the nation and the world as this historic year draws to a close, the only certainty is that both obstacles and opportunities will continue to challenge biopharmaceutical companies, regulatory authorities, and the research community in the months ahead.

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**FDA Identifies Essential Medicines for U.S.**

As part of the administration’s campaign to reduce U.S. reliance on an increasingly global pharmaceutical supply chain and to minimize potential shortages for critical drugs, FDA has published a list of those drugs and medical products considered critical for addressing public health emergencies. The list will provide a basis for bolstering biopharmaceutical production at home of essential medicines and medical products and for addressing supply chain vulnerabilities (see: https://bit.ly/36qsbS8).

The White House launched this process with an executive order issued Aug. 6, 2020 (see: https://bit.ly/37pVL2J) instructing FDA to develop the essential medicines list in 30 days. The resulting list includes 233 drug and biological products and active pharmaceutical ingredients (APIs) for treatments able to protect against emerging infectious diseases plus chemical, biological, radiological and nuclear threats. An additional list covers 96 important medical devices such as diagnostic testing kits, PPE, monitoring devices, ventilators, and items for vaccine delivery (see: https://bit.ly/3mv8b6m). The listed products are identified as those most needed for treating patients in acute care medical facilities and for responding to future pandemics and biomedical threats.

To bolster purchases of U.S.-made drugs, the program also calls for federal agencies that fund healthcare programs to favor domestic sources in purchasing essential medicines. FDA is coordinating government-wide efforts to acquire listed products, identify supply chain vulnerabilities for these products, and to support advanced manufacturing and innovative technologies likely to bolster the competitiveness of U.S.-based manufacturing compared to foreign countries. The August executive order also calls for FDA to accelerate the approval of U.S.-made essential medicines and to refuse entry into the U.S. of products from foreign plants that have blocked FDA inspections. Moreover, the administration looks to streamline environmental and other regulations likely to curb domestic biopharma production.

FDA seeks comments from manufacturers and other stakeholders on the criteria it used to develop the essential medicines list, on additional medicines and products to include on the list, and on how often the list should be reevaluated. It’s general criteria for listing essential medicines includes both acute-care treatments and those needed for longer-term health management, with a preference for dosage forms most commonly needed in acute care facilities (see: https://bit.ly/36pbvld). Where multiple drugs might be available, FDA looks for treatments for the widest population, for multiple conditions, and those with unique safety profiles.

— Jill Wechsler
The Ever-Changing Face of NICE Guidance on Drug Innovation

The U.K. is firmly and definitively on its way out of the EU within weeks, but in one respect at least its influence will persist, with the internal reflections of its influential NICE (National Institute for Health and Care Excellence) continuing to shape thinking across the continent, and beyond, on reimbursement of new medicines—and consequently on drug development programs everywhere. So nobody in Brussels or member state capitals is going to ignore the latest methods review from England’s health technology assessment body.

The aim of the recently-published proposals (see: https://bit.ly/36aHXMz) are to bolster the ability of NICE and its evaluation committees to support introducing valuable innovative technologies, and the consultation paper on the case for change ranges widely across issues a crucial as acceptance of risk, the modifiers relevant to judgments of value, and the use of real-world evidence.

NICE is considering removing its currently-used modifier for life-extending treatments at the end of life, and replacing it with a modifier better suited to valuing the benefits of health technologies, based on the severity of the disease. The change would be more broadly and fairly applicable than the previous end of life criteria, and “more accurately reflect society’s values,” it says. It argues that there is limited evidence that society places additional value for life-extending treatments at the end of life, and greater evidence that society highly values health benefits in very severe conditions.

The new modifier would focus on the severity of the condition with current treatment, implicitly encompassing concepts such as the burden of illness and the degree of unmet need. And because of the overlap between severity of disease and end of life conditions, severity can work as a quantitative modifier that operates similarly to the current end of life modifier, NICE believes—although it acknowledges that “further work is needed to confirm how such a modifier should be defined and implemented.”

There are no plans to introduce a specific modifier for rarity, despite wide public support for attention to rare diseases, but so that “people with rare diseases are not disadvantaged and that technologies for these conditions are supported,” NICE is also proposing to adopt a more accepting attitude to uncertainty in this context. “Uncertainty should remain an important consideration in decision making,” it says, and should be even more acceptable in some defined circumstances—notably where evidence generation is complex and difficult, and particularly in rare diseases. The concept should also apply to innovative technologies, technologies that provide large benefits, and when the uncertainty and risks can be monitored and controlled, such as in a managed access arrangement, it goes on. Amendments to the description and characterization of uncertainty, along with clarifications on how it should be taken into account as a modifier, are intended to permit a more robust and nuanced approach to risk for new technologies. Technologies recommended should always provide valuable health benefits, but greater flexibility could be exercised in identified priority areas—which includes, it says, “developments in commercial and managed access arrangements.” Evaluations should include an overall assessment of uncertainty, including the effects of different types of uncertainty, whether uncertainties have been captured in analyses, and whether uncertainties can be addressed by additional evidence.

The review also considers the challenges that NICE faces in “fairly, efficiently and robustly” evaluating innovations in emerging technologies such as advanced therapy medicinal products or histology-independent cancer treatments. The objective is to secure rapid access to valuable innovations, and the changes envisaged to evaluation methods should “create a more receptive environment for emerging health technologies,” says NICE. However, in all cases, the ultimate aim is improving the health gain from spending on new innovative medicines: “We should be aware of the effect of any methods changes on healthcare spending and on how healthcare resources are prioritized,” it underlines.

NICE is leaning towards greater acceptance of the “valuable resource” of real-world evidence as “it is particularly important in the current health and technology landscape.” It sees its merits in providing information on the generalizability of trial evidence in clinical practice, in supplementing and adding to clinical trial evidence when trial evidence is limited, in describing populations, patient groups, and clinical practice, and in describing the experiences of people with particular conditions and having particular treatments.

Evidence requirements for surrogate outcomes should also be updated to include information on different levels of evidence, expectations for evidence of validation, and how to account for uncertainty, and should include flexibility for surrogate outcomes in different evidence scenarios. Outcome measures should be selected in consultation with people with the condition or disease, since “patient-reported outcomes can capture important aspects of conditions and interventions, and should be appropriately validated and the methods used clearly reported.”

Other changes envisaged are guidance on comparators and on agnostic tumor treatments.
When clinical trials do not include a comparator group, several methods to derive comparative evidence should be explored, says NICE. And it urges that histology-independent indications should be treated as a single indication and not as a collection of tumor-specific subgroups. Challenges of heterogeneity, generalizability and unrepresented groups are common to many evaluations, although to a different degree, it says, and heterogeneity across tumor types is “an important theme,” it says. This raises also the issue of generalizability from clinical trials to clinical practice. However, in practice, it concedes, “it will be difficult to justify not considering different tumor types to a significant extent in the evaluation,” so “any assumptions about homogeneity, heterogeneity and generalizability to clinical practice must be clearly presented, tested and fully explored.”

NICE says it will “consider responses from stakeholders” and then develop a structured decision-making framework which will include the changes in an updated program manual. Further phases of methods review are already envisaged for genomics, digital technologies and antimicrobial resistance technologies. The consultation also notes that the case could be made to changes how to value costs and health effects for health technologies in the future through the NICE discounting methodology. However, the policy and affordability implications go beyond the reach of the present review and will need to be considered separately before any change could be implemented, it says.

**EUROPEAN COMMISSION CALLS FOR EXPRESSIONS OF INTEREST FOR COMP**

The call aims to fill three positions for the Committee of Orphan Medicinal Products (COMP) members nominated by the European Commission to represent patient organizations. These members participate in the meetings of the Committee alongside the members nominated by each Member State, Iceland and Norway, as well as an additional three members nominated by the European Commission based on a recommendation from the EMA.

The three members representing patient organizations will be appointed for a term of three years from July 1, 2021, which can be renewed. The deadline for the submission of applications to the European Commission is December 18, 2020.

The COMP’s main task is to examine applications sent by companies and decide whether their medicines can be designated as ‘orphan.’ An orphan medicine is used in the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare, which means it affects no more than five in 10,000 people in the EU.

The role of a patient organization representative in the COMP is to give a voice to patients and ensure their needs are taken into account in the Committee’s decision-making process.

Representatives of patient organizations participate in the COMP procedures in the same way as other Committee members. They are expected to attend monthly Committee meetings at EMA and to actively contribute to scientific discussions, examine documents and make comments with a specific focus on the target group they represent.

The European Commission will appoint the patient organization members after consultation with the European Parliament.

**EMA Receives Application for CMA of Moderna Vaccine**

On Dec. 1 EMA received an application for conditional marketing authorization (CMA) for a COVID-19 mRNA vaccine by Moderna Biotech Spain, S.L. The assessment will proceed under an accelerated timeline. An opinion on the marketing authorization could be issued within weeks, depending on whether the data submitted are sufficiently robust and complete to show the quality, safety, and effectiveness of the vaccine.

Such a short timeframe is only possible because EMA has already reviewed some data on the vaccine during a rolling review. During this phase, EMA assessed data from laboratory studies and also started assessing data on immunogenicity (how well the vaccine triggers a response against the virus) and safety from an early study.

EMA will now assess the data submitted as part of the formal application for CMA. The Agency and its scientific committees will continue working on the assessment over the next month. If the data submitted are robust enough, EMA’s scientific committee for human medicines will conclude its assessment during an extraordinary meeting scheduled for Jan. 12 at the latest.

—Wire reports
Industry Forced to Rethink Patient Participation in Trials

The COVID-19 pandemic has brought new attention to clinical trials and is forcing the industry to rethink the best ways for patients to get involved. On Sept. 29, W2O announced the launch of Hū, a first-of-its kind Patient Activation Organization to accomplish just that.

In this interview, EVP and General Manager of Hū, April Lewis, discusses why the industry is seeing such a large drop in trial participation, how COVID is affecting trials, and what Hū is doing to better humanize trials.

Andy Studna: You have 20 years of experience in the field of innovating trial operations. What do you think are the most valuable lessons you can take away from that time that are helping you in your current role?

April Lewis: There are three things that I’ve learned that I carry with me. One, when we think about innovation, timing is everything; even the best innovations have to be met with a level of market readiness, adoption readiness, or maturity of a market in order to be successful.

The second thing is that data and evidence are only part of the story. As an industry, we’ve failed often because we look at data as the answer, when really it should be looked at as prescriptive guidance. I think data and evidence become most valuable when it’s balanced with experience and even sometimes instinct.

The third thing that I keep at the forefront of my mind is that patients aren’t waiting for us. If we stop and consider a trial, as we would consider a product, we have to think about whether or not that product is something that’s attractive. We take that approach with sites, so we often focus on whether or not a study is attractive, but we don’t take that same approach with patients. Thinking about what’s in it for patients is the thing that’s been missing.

AS: The willingness to participate in trials has plummeted from 85% to just about 49% in the past year (CenterWatch). Why do you think we’ve seen such a drastic drop like that?

Lewis: There’s copious amounts of misinformation around the pandemic; that’s leading people into a state of paralysis and fear. I see it as an opportunity for R&D organizations to band together, change the narrative, and create a unified message.

AS: Do you think that more literacy around trials will help people warm up to them and if so, why?

Lewis: Knowledge is power. Right now, people’s knowledge is wrapped up in a lot of noise. I truly believe we could fix that if we did a better job of providing resources to the general public around the value of trial participation. For example, what it means for our ability to future-proof care options by participating and some of the practicalities of participation, we’d really move the needle. However, this is a conversation that isn’t a one-size-fits-all, and requires us to not only combine forces as an industry, but to be consistent in our messaging, and keeping in mind that we need to personalize the conversation with patients in order to stay engaged.

AS: How will Hū be utilizing social and behavioral evidence to increase patient participation in trials?

Lewis: We’ve built a model that predicts which patients have the highest intent to participate and it has shown high correlations. In addition, when we look at other industries, behavioral economics techniques have increased desired action by 41%. I’m not suggesting that we’ve been able to achieve that metric yet, but in other industries behavioral economics has been able to influence action and increase it to the desired state by 41%. So, we’re building out our tools and our techniques to leverage behavioral economics to provoke action in the same ways. For example, we are building out an innovative platform for gamified, scaled, digital patient insights. It’s a technique that’s going to highlight patient preferences and motivations that can be used by study teams in study design and delivery. This is a massive shift from the professional patient advisory board that gets used today. The third thing we’re using social and behavioral data for is working on a model to predict patient participation. This will allow us to predict what patients have highest interest or intent to participate, but the next step is translating that into enrollment rates. If we’re able to achieve that projection and prediction methodology, that will be a huge game changer.

AS: What do you think are the most important elements for any company to consider when it comes to humanizing these trials?

April Lewis EVP, General Manager, Hū

If we can combine listening with evidence and data, we can start to have a strategic conversation that personalizes the way we engage with patients more effectively.
Lewis: The most important elements start with listening and learning. We need to do a better job in understanding the patient lexicon; giving consideration to ethnic insights and the patient motivations. If we can combine listening with evidence and data, we can start to develop and analyze, get to a strategic goal, and have a strategic conversation that personalizes the way we engage with patients more effectively. The tactics are the last thing; by doing the upfront work and understanding the patient, adding in the evidence, and getting to that conversation blueprint, that allows us to build tactics that are going to have more meaningful effects on the ability to not only motivate a patient to participate, but to maintain that motivation throughout the trial.

AS: How do you think that the pandemic has shed more light on the issue of the decreasing participation in trials?

Lewis: I think COVID has brought light to participation in clinical trials in general and has brought conversations about them to the table. I think that participation is a systemic issue and it requires a systemic response. We know, for example, if we think about diversity and inclusion in trials, there’s been under-representation of underserved populations for many years, but COVID has really brought this to light in particular. COVID has also brought to light the complexities and the reasons that are multifaceted; things like skepticism, lack of trusted relationships, and questionable data. Our approach at Hū is one that considers partnership as a balanced approach to not only civic and community engagement and partnership, but balancing that with medical and pharma partnership, as a means to take that systemic response.

—Andy Studna is an Assistant Editor for Applied Clinical Trials

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TOP 5 SOCIAL MEDIA


eLEARNING:

COVID-19 required the life sciences industry to rapidly embrace decentralized clinical trials (DCTs) to keep clinical research moving forward during the pandemic. This virtual approach helped the industry maintain continuity in research while meeting the needs of patients in their homes. The forced transition caused many sponsors to realize the benefits of a decentralized model. In this webcast, we will explore the changing roles played by sponsors, CROs, site staff, and other stakeholders in DCTs—and how to ensure patients still get the support they need in these virtual research environments. https://bit.ly/3qktqdw

The types and sources of clinical trial data streams are increasing dramatically in both volume and variability along with decentralized trial designs. The combination of increasingly complex protocols and expanded clinical data streams have created the perfect storm to accelerate transformation in data management. In this “D-Clinical Age”, leveraging modern technologies and new approaches and mindsets is required to accelerate the development of new treatments. This webinar will examine how data management can drive digital transformation with the right mix of technology, skills and process redesign. https://bit.ly/2VD8ujG
Public Trust and the 'Last Mile' for COVID-19 Vaccines

Battle for trust ensues as vaccines are set for approval

Throughout the pandemic, the global public has had a front-row seat in an emotional theater of drug development. Daily news updates and more in-depth profiles have covered scientific breakthroughs, new collaborations, commitments, clinical trial activity, and preliminary results from interim assessments. And, as a result, public awareness of the role and importance of the pharmaceutical industry has increased sharply and public perception has improved dramatically.

This is a unique moment and a rare opportunity for drug development stakeholders to hit the reset button and enter a higher level of partnership and engagement with the public and patient communities. But until now, the pharmaceutical industry has largely emphasized one side of the story. The focus-to-date has been inward—on the industry’s innovativeness, productivity, passion, and commitment.

With late-stage vaccinations in the process of receiving Emergency Use Authorizations (EUA), the clinical research community in collaboration with public health officials and the clinical care community—needs to expand its focus outward to collectively engender trust and support for the great science that the world is witnessing.

In addition to conveying gratitude for study volunteers who participated in COVID-19 vaccine and treatment clinical trials, the clinical research enterprise must also demonstrate respect for the public and patients through complete transparency and disclosure, in plain language, of the results of its COVID-19 clinical trials; and it must provide consistent and easy-to-understand patient and public education focusing on the “last mile” between the availability of safe and effective new vaccines and the societal importance of, and obligation in, their uptake.

Reputation rebirth

As early as this past April, Pew Research reported growing public support for the pharmaceutical industry. This could not have come any sooner. Only eight months earlier (September 2019), Pew Research reported that the pharmaceutical industry was the most poorly regarded of all industries, having finally received the lowest rating of all those evaluated. Many may recall a Pew Research study published several years ago showing that the pharmaceutical industry’s reputation had fallen sharply putting it on par with the oil and used car industries.

In July 2020, the Harris Poll conducted among several thousand Americans noted that 54% gave the pharmaceutical industry positive ratings. This was a remarkable 22 percentage point increase above the results that Harris had reported in February 2020, one month before widespread lockdowns went into effect. Harris noted in its report that pharmaceutical companies were “…the only industry to sustain reputation gains through the pandemic. While other industries—such as grocery, retail, technology, consumer products and financial services—also rose during the spring and summer, most spiked in May and have since flattened or dropped back to typical pre-COVID levels.”

And a global poll conducted by Caliber Research in September 2020 reported that public perceptions of the pharmaceutical industry had improved measurably around the world. The poll solicited responses from more than 13,000 people. Caliber noted that “COVID-19 is playing a very important role in reminding people of the [pharmaceutical industry’s] importance and relevance, especially in markets like the U.S. where the pandemic’s positive reputational impact has so far been the greatest.”

Progress without clarity

Between April and October 2020, news coverage of coronavirus drug development activity appeared several times per week. Beginning in early November, however, daily coverage became the norm as preliminary results of late-stage COVID-19 vaccine trials, funded by Operation Warp Speed, were publicized. Pfizer-BioNTech was the first to announce in early November followed by Moderna in mid-November and AstraZeneca-Oxford University later in the month. In December, regulatory agencies including the FDA’s Center for Biologics Evaluation and Research (CBER) will begin making decisions with regards to EUAs. Through the Operation Warp Speed program, drug and biologic development will be more than 80% faster than the typical clinical duration for vaccines.

A number of nongovernmental committees and panels are providing input and expertise to inform emergency access and approval, as well as vaccine distribution and logistics decisions. These committees include the Vaccines and Related Biological Products Advisory Committee (VRBPAC), which provides input into EUAs and approvals of vaccines. The Center for Disease Control’s (CDC) Advisory Committee on Immunization Practices (ACIP) provides input into the distribution of vaccines and their use. In partner-
ship with these committees, CBER and the CDC have far greater public transparency.

Collectively, these agencies and committees now face the difficult task of facilitating unprecedented development and commercialization speed while reassuring the public that no corners have been cut and that these treatments and vaccines are in the most competent and capable hands.

Operation Warp Speed leadership has yet to clearly indicate publicly how COVID-19 vaccines will be allocated. And although ACIP, the CDC, the National Academies, and outside consultants have all been meeting to discuss prioritization of COVID-19 vaccines when they are available, lack of clarity and simple messaging tailored to the lay community has contributed to speculation in the media and ultimately public confusion and concern. At the outset of the pandemic, public confusion and concern began mounting—and has not abated—with the poor availability and apparent mismanaged distribution of personal protective equipment and the antiviral medication remdesivir.

Transparency and trust

The majority of the public worldwide supports vaccines. But a vocal minority—very often without rational or scientific basis—is against vaccination. Concerns over a link between vaccines and autism, for example, persist despite scientific evidence to support it. Public confidence in vaccines varies by country and by communities within a given country.

The media tends to exacerbate the problem. They report adverse patient conditions and/or patient deaths associated with the time of a vaccination, but not the results of investigations into the cause of death. These investigations, completed long after misinformation has been in circulation, typically show that the condition and/or death was unrelated to the vaccine.

For COVID-19 vaccines to be widely embraced and to deliver on their promise, they must engender public confidence and trust. Clinical research and healthcare professionals must ensure that their messages about vaccines and their distribution are balanced and transparent in depicting risks, benefits, and uncertainties. Messages must also be customized to the community that they target. Plain, non-technical, tailored communications in the mass and social media will go far in helping to build this balance and transparency. Consistent and simple—but not oversimplified—communication is essential. Creative communications developed by a collective of major advertising agencies will be highly valuable input here.

Media briefings will also prove helpful as many reporters have little to no background in medical research and healthcare. Partnerships with patient advocacy groups will also help ensure that communications reach a broader community via sources that are perceived as trusted and credible.

Producing and distributing plain language summaries of COVID-19 vaccine clinical trial results will also play a major part in building public and patient trust. At this time, the pharmaceutical companies leading Operation Warp Speed late-stage vaccine trials have signaled their primary intent to publish the results of their clinical trials in medical journals and on the NIH ClinicalTrials.gov registry. But this is not enough. These channels are primarily geared toward the scientific and medical community. Plain language summaries should be disseminated—simultaneously with the publication of technical summaries—to patients who participated in the clinical trials through public-facing healthcare communication channels, patient advocacy groups, mass media outlets, and digital and social media.

Despite unprecedented investments in vaccine development and distribution, public confidence in COVID-19 vaccines is hopeful but tenuous. This is due in large part to historical context, the lack of clarity and transparency from government agencies and the clinical research and healthcare professional communities. It is also due to the spread of misinformation since the pandemic began.

Global vaccination programs that rid the world of COVID-19 will succeed only if there is widespread belief and trust that these vaccines are safe and effective, that policies for prioritizing and executing their distribution are equitable and rational, that every individual has an important part to play. Translating the scientific progress and promising new vaccines into successful vaccination programs will require overcoming the significant challenge of building public trust and confidence through frequent, comprehensive, consistent, customized, balanced, and straightforward communication and education.

—Reach Ken Getz via email at kenneth.getz@tufts.edu
Importance of Diversity in Parkinson’s Research

Eliminating barriers to engage underrepresented populations.

The Michael J. Fox Foundation for Parkinson’s Research (MJFF) aims to speed clinical research by removing obstacles that stand in the way of drug development. In pursuit of this mission, the Foundation gathers insights from a wide range of stakeholders and uses these perspectives to enhance clinical trial processes from start to finish. In *Applied Clinical Trials*’ Eye on Patient Advocacy series, we will share best practices and lessons learned from the field of Parkinson’s research that can be applied to clinical trials across disease states. In our latest column in this series, we explore the importance of addressing barriers to participation for historically underrepresented and marginalized groups.

**Background**

Despite growing emphasis on increasing diversity in clinical research, the proportion of underrepresented groups (URGs; defined in this study as women and gender minorities, racial and ethnic minorities, individuals earning below a median household income of $57,000, a high-school education or less, and/or rural residents) in Parkinson’s disease (PD) research remains low, with as many as 91% of participants identifying as non-Hispanic Caucasian in various studies.1–3 Although some studies, such as the MJFF online PD research platform Fox Insight (FI), have been designed to reduce or eliminate research barriers for URGs, equitable representation in PD research remains elusive.4 Without diverse inclusion in these trials, estimates of PD disparities in underrepresented populations, which remain poorly understood, may widen.5–7

Although the barriers to PD clinical research among underrepresented populations have been well identified, it remains unclear whether suggested interventions from the existing literature will improve engagement of traditionally underrepresented populations in PD research. For these reasons, MJFF sponsored the Fostering Inclusivity in Research Engagement for Underrepresented Populations in Parkinson’s Disease (FIRE-UP PD) Study to 1) explore whether it is possible to identify best practices to engage URGs in PD clinical research, 2) to assess knowledge and attitudes toward clinical research designs, and 3) to increase participation of URGs to FI.

**Study design**

**Method**

A request for proposals (RFP) was released for academic medical centers within the Parkinson Study Group research network to participate in FIRE-UP PD. Sites were instructed to identify a specific URG or geographical region to focus on, a specific barrier to PD research participation experienced by this group as categorized by the Picillo PD research barrier framework8, and a specified intervention as categorized by the Picillo et al. framework. Eight participating sites were selected, and were paired based on their proposed interventions and randomly assigned to either intervention or control conditions. Sites in Chicago, Boston, Denver, and Southern Florida were assigned to the intervention condition and were given $45,500 to execute their proposed design, whereas a second site in Chicago, the rural northern Midwest, the greater Seattle metropolitan area, and San Francisco were given $10,000 to serve as passive controls, maintaining their current recruitment workflow. Interventions included developing educational tools and surveys to engage community health centers in PD diagnosis (Boston), partnerships with local PD support groups to discuss PD research (Southern Florida), developing multi-stakeholder alliances and focus groups to create community-specific educational toolkits (Chicago), and recruiting community stakeholders to reimagine medical and research information for the community through a collaborative method called Boot Camp Translation (Denver).

The study was divided into three temporal phases for all sites: pre-intervention, to establish a recruitment baseline; intervention, to deliver a specified intervention or in the case of control sites, to continue passive recruitment activities, and post-intervention, to determine change from baseline. In addition to recruitment measures to...
FI, the FIRE-UP PD study was designed to collect survey responses from participants with regard to awareness and trust of PD research. Sites collected the Trust in Medical Research Scale (TIMRS), the Patient Engagement in Research Scale (PEIRS) and PD Research Participation Surveys, which assessed specific PD research designs and their impact on participation willingness. All sites also collected barriers to PD research participation, capturing reasons why URG individuals, who would otherwise participate in FIRE-UP PD, could not do so. All sites displayed FI recruitment materials as designed by MJFF and had a dedicated tablet device for FIRE-UP PD surveys and FI registration.

**Results**

The FIRE-UP PD study enrolled 488 individuals across the eight sites (intervention n=295), while 230 individuals (intervention barrier n=101) faced insurmountable barriers to participation, outlined in Figure 1.

Changes in trust, measured via TIMRS did not significantly improve for intervention sites relative to control sites, although a trend towards improvement emerged, t(382)=1.80, p=.073. There was no disproportionate change in patient engagement or in overall research participation willingness for intervention relative to control, all ts < 1. However, participant characteristics indicated that intervention site participants were significantly more diverse at both pre- and post-intervention with respect to race, ethnicity, income, and educational attainment.

Diverse accrual to FI (n=181) improved across all sites over the study period relative to sites’ own baselines, although intervention sites significantly improved diversity with respect to race, ethnicity, income, and educational attainment, while control sites improved race and ethnic diversity alone, as seen in Figure 2.

**Conclusion**

The FIRE-UP PD study was designed to measure barriers, attitudes, and FI accrual for URG populations accessing PD clinical research. The study suggests that URG recruitment could have increased by as much as 50% if common participation barriers such as language, time, and the digital divide were addressed. Although sampling and selection factors obscured trends in the attitudinal surveys, intervention sites recruited a broadly diverse sample of participants to complete surveys as well as enroll in FI, despite intervention sites’ focus on a single URG. Notably, although control sites were instructed to continue their baseline recruitment activities, nevertheless these sites yielded increased racial and ethnic diversity in FI. This suggests that while targeted interventions may yield substantial benefits to improved diversity of PD research participation, merely orienting to the problem of lack of study representativeness may alter even passive recruitment practices in subtle ways to promote more inclusive research participant cohorts. Developing detailed recruitment protocols that focus on particular URG populations as well as barriers faced by these groups may be a promising addition to PD research, although future studies will need to better understand specific mechanisms of efficacy and comparative effectiveness given similar site and study characteristics.
References

—Authors of this report: Jonathan Jackson, PhD, Angie Sanchez, MD, Juliana Ison, and Helen Hemley, all with CARE Research Center-Massachusetts General Hospital; and Bernadette Siddiqi, MJFF

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The MJFF Research Engagement Team includes James Gibaldi, MS, Associate Director; Tara Hastings, Senior Associate Director; Catherine M. Kopil, PhD, Director; Bernadette Siddiqi, MA, Associate Director; and Michelle Whitham, Research Partnerships Officer at The Michael J. Fox Foundation in New York, NY. To contact the MJFF Research Engagement Team email: trialsupport@michaeljfox.org

Past Columns in Series
The Importance of Site Selection
The Systemic Synuclein Sampling Study (S4) was a multicenter, cross-sectional, observational study sponsored by MJFF. The primary objective of this study was to better understand the progression of Parkinson’s disease (PD) by identifying the optimal biofluids and tissues for measuring the protein alpha-synuclein outside of the brain as a potential biomarker in individuals with PD. The secondary objective of the study was to create standard operating procedures for the collection and assessment of multiple tissues and biofluids to better understand alpha-synuclein’s potential as a biomarker for PD. [https://bit.ly/3gjUchH](https://bit.ly/3gjUchH)

Overcoming Transportation Barriers
In January 2017, MJFF launched a survey to assess the need for transportation infrastructure at clinical trial sites. Data from the survey was used to inform the design of a transportation intervention that was tested via the Parkinson’s Disease Trial Recruitment Innovation (PD-TRI) project, an MJFF-funded pilot study aimed at reducing barriers and enhancing facilitators to clinical trial recruitment. [https://bit.ly/39OzV2p](https://bit.ly/39OzV2p)

Retention Strategies: A Case Study
Patient retention is an important element of the Parkinson’s Progression Markers Initiative (PPMI), a landmark, longitudinal, observational study sponsored by MJFF. PPMI aims to find reliable and consistent biomarkers for PD progression by studying cohorts of Parkinson’s patients, populations at risk for PD, and controls without PD. [https://bit.ly/3gjUchH](https://bit.ly/3gjUchH)

Building a Physician Referral Network: A Case Study
General practitioners often are not involved in the recruitment strategy for clinical trials. Historical barriers have made engagement with physicians challenging. They may fear losing care of patients to clinical trial site providers, be unfamiliar with the trial and principal investigator (PI), or have concerns about jeopardizing the doctor-patient relationship. One approach to building trust and overcoming these obstacles is for research institutions and PIs to actively engage with community physicians. [https://bit.ly/2VLK0mX](https://bit.ly/2VLK0mX)
Regulatory Data: How Technology Can Help ClinOps Survive

Clinical operations professionals, burdened by lack of data standardization, turn to technology in hopes of streamlining regulatory processes for the future.

As clinical trials grow in complexity, clinical operations (ClinOps) professionals are finding it challenging to keep pace and fulfill their oversight responsibilities. Their workloads are increasing like never before, and their resources are not helping them keep pace with a tsunami of data, much of it unstructured. One of the central areas of data requests come from their internal company colleagues in regulatory, for data that regulatory bodies will eventually require, as well as data requests from regulators themselves.

Mike McLaughlin, Associate Director of Clinical Operations at Dermavant Sciences, Inc., says the major ClinOps issue is dealing with large amounts of data and a lack of standardization. “It was much simpler when we dealt with paper files and not electronic data,” he says. “Now we have to sift through and streamline the data and find the data that provides the most value.

“Different companies collect data in different formats. For example, there’s a recommended DIA file structure and format for the TMF, but not all companies file documents using the same file structure,” McLaughlin explains. “It is more difficult to review the TMF if the documents are not structured and formatted correctly. Time-consuming manual labor is needed to correctly structure and format the documents. Software could speed this task.”

Karen Roy, Co-Chair of the DIA-founded Trial Master File (TMF) Reference Model and Chief Strategy Officer at Phlexglobal, a technology and services organization for clinical and regulatory matters, continued: “I think the biggest challenge is that the regulators want to see the detail behind the documentation, including the different systems and audit trails that back up the documentation and (ClinOps) activities. It’s no longer just a matter of providing a few documents to review. This has made the TMF much bigger because people don’t know exactly what they should be collecting or presenting to regulators. They collect way more than they used to, and sometimes more than what’s needed. Mandates have made it harder to keep up from a regulatory perspective.”

“There’s pressure on clinical operations to produce data in a consistent, manageable, and compliant structure for their colleagues in regulatory affairs and operations to streamline submissions. But there are different mandates to follow, such as the Electronic Common Technical Document (eCTD) for the FDA. It’s challenging, especially when you have mandates within mandates creating duplicate work,” adds Jim Nichols, Co-Chair of DIA’s Regulatory Information Management Committee and Chief Product Officer at Phlexglobal. Roy and Nichols add that sometimes the mandates are not clear, leaving ClinOps in the lurch.

Poor metadata compliance

Paul Fenton, President and CEO at Montrium believes there has been poor compliance with registering metadata against documents because the process is very labor-intensive and ultimately, “We don’t fully leverage the metadata as an information source. We can scan documents using AI and identify a broader range of metadata that could be extracted from those documents and used to provide a richer base of information about particular types of documents, a particular trial site, or a particular process,” he states.

Several companies are developing AI solutions to recognize documents and metadata, make them more structured, and perform automated extraction on indexing of information. He expects to see these types of systems, which are much more integrated and process driven, with AI and machine learning tools built in, in the next two to three years.

In addition, development of a forms management solution, which would be part of the TMF, would allow companies to collect and add data in a much more structured way directly into a database, according
to Fenton. “When you initiate a site, there are many forms that must be completed, which provide basic information about that site, like FDA Form 1572. These forms could be filled out electronically online instead of being uploaded as a document, which would make the data easier to integrate and exploit,” he says.

Fenton chairs a group which has developed a standard for exchange of TMF information between systems, cTMF Exchange Mechanism Standard that is a sub-group of DIA’s TMF Reference Model. They have started to define areas like standard metadata, which is a step toward having more standardized information about operational documentation.

“There’s a lot of variability in terms of the information we have to manage,” Fenton continues. “There are probably around 500 different types of documents collected in a TMF, which all have their own format, and formats can change from one company to the next. Standardization will help, and machine learning could help unlock the gold mine that all of that information represents.”

Jim Reilly, Vice President, Vault R&D, Veeva Systems, said, “Why can’t we use AI in the form of natural language processing or machine learning to examine content as it comes into a TMF and automatically classify and attribute metadata to the documents so that we don’t have to spend much resource time reviewing material that’s already been received? This would be a tremendous cost and time saver.”

**The CRO/sponsor data flow**

Although requiring more effort on the part of sponsors and CROs, McLaughlin thinks it’s important that the FDA wants more sponsor oversight and is placing more emphasis on quality. “The current guidance (ICH E6 (R2)) is more specific than in the past. They’re driving home quality and risk assessment to make sure that clinical trials are performed with care.”

In the guidance document, the FDA updates and further outlines responsibilities of institutional review boards (IRBs), investigators, and sponsors based on “evolutions in technology and risk management… to increase efficiency and quality.” The goal is to improve clinical trial design, conduct, oversight, human subject protection, and the reliability of trial results.

“Sponsors must review documentation on a regular basis, ensuring that CROs are following good clinical practice. As sponsors, we’re responsible for making sure that the obligations that you’ve transferred over to the CRO are being fulfilled,” McLaughlin notes.

“It’s incumbent upon sponsors to be accountable for their trial execution even when they outsource. So, it’s important for them to have a mechanism by which they can accurately receive information from their service providers. Technology can have a significant play here,” explains Reilly.

He thinks that technology needs to “up its game” and provide a consistent mechanism that enables CROs and sponsors to share and exchange information, driving better trial oversight. Part of this involves having better operational data standards and consistent data standards, but he also believes there is a need for technologies that have open connection points, and which are networked so data can flow between CROs and sponsors and be better understood by the receiver.

**Quality and AI principles**

There is discussion of using artificial intelligence (AI)—as in many areas of pharma—to build quality into unstructured and structured documentation that becomes part of the TMF. “Regulators are increasingly supporting the use of Quality by Design principles (QbD) in clinical trials. Risk-based quality control is a key component of QbD,” Roy explains.

Addressing risk management and taking a risk-based approach pushed by regulators is important for Fenton. But clinical trials contain a lot of information.

“A clinical site might be higher risk because they’re recruiting a lot of patients, or there may be many safety cases at that site, or delays in providing information that can impact risk. We should be able to flag groups of documents or information that should receive additional scrutiny, QC, or verification because they’re considered an inspection risk. Machine learning could improve the risk models over time,” explains Fenton.

While AI can be used to check documentation for quality and to help with risk assessment, there also is a need to collect data from disparate sources more efficiently and to unify the data collection process. “Companies haven’t been the best at building quality into documentation from the beginning and putting
processes, such as the ALCOA framework, into their systems,” states Roy. She suggests adding ALCOA and other quality processes to source systems and then using AI to analyze the documents and transfer them to the centralized TMF, which would be more efficient.

It’s also important to map out what technology can do. Technology can bring things together and indicate knowledge and data gaps. But it won’t tell you which documents are needed, unless it is directed to that need. This is a skilled task that requires the expertise of the ClinOps team, or outside experts, adds Roy. And that subject matter expertise can be built into technology to essentially establish a risk-based approach to a process to check on documentation.

Other AI approaches
McLaughlin is hopeful that advanced software, such as AI and machine learning, will remove some of the burden from ClinOps personnel, for example by helping to structure any unstructured data, optimizing documentation in the TMF, and by helping trial participants remain compliant with their medications. But he thinks the technology still requires additional commercial exposure before it can fully demonstrate its usefulness in clinical trial settings.

“ClinOps people can do many tasks but they are struggling to keep pace with regulatory requirements,” Nichols explains. “Compliance is taking up more time and effort from trained people to do manual, repetitive tasks. These tasks are tailor-made for AI technologies, such as machine learning.”

To connect the dots of the ins and outs of the trial, including the many different study events, Fenton indicates a standard process model could be established that defines all of the processes that occur in a clinical trial, including the events that trigger them and the data required to describe them. This model would then be used to pull information from different sources.

“Technology can help by leveraging this model. But the model needs to be defined by people who know about clinical processes and by the regulations,” Fenton says. “We can improve the model over time by making connections between different processes and events as well as looking at historical data through machine learning and AI.”

Another related technology trend Alok Tayi PhD, Vice President of Life Sciences at Egnyte, sees is the emergence of natural language processing (NLP) in the clinical trial space. “NLP promises to automate rote tasks and improve data integrity by helping staff extract key data from study reports, CVs, and other documents,” explains Tayi. Recent advancements in NLP enable software to perform cognitive tasks, like document classification, data extraction, and even summarization. Tayi believes that these novel capabilities, integrated into the trial workflow, will allow trials to process quickly new data, check for inaccuracies, and extract insights quickly.

Reilly is encouraged by how the FDA and other regulators are piloting initiatives that can make the review process less difficult. The agency’s Real-Time Oncology Review Pilot Program aims to explore a more efficient review process which includes companies submitting top line results as they occur, speeding the review process.

“In many ways they’re pushing along the data directly to the agency rather than compiling it in a big package. Technology can help with modern submission tools and mechanisms where data can be compiled in a normalized sense and pushed into the regulatory system. A more hardened connection between clinical and regulatory can make a real-time submission process more efficient,” Reilly explains.

AI and data privacy
Tayi expects AI algorithms will help the industry address key data privacy issues. AI can help sponsors, sites, and CROs monitor their data for sensitive information and ensure compliance in an automated fashion. For example, technology can ensure that consent documents are properly classified, or that data managers are alerted to personally identifiable information (PII) embedded within the metadata of CT imaging. “But we need clarity on how to train the models to help identify data as well as very specific regulations to which we can tie the data,” Tayi notes. He also sees AI helping structure data and metadata for one’s TMF.

In addition, as sponsors and CROs consider running new types of trials, such as virtual clinical trials, data privacy risks are heightened. According to Tayi, institutions will need automation and AI software that ensures that the right people have access to the right data, without the overhead and burden to the team.
Clinical research & development is at a crossroads, requiring new approaches to deliver drugs to market faster — with less cost — while mitigating risk, and without compromising safety or quality. The market is moving towards risk-based monitoring (RBM) to monitor clinical trials as it provides new levels of efficiency and quality while providing predictability of speed and operational outcomes.

Register today for this free webinar to learn how RBM applies advanced analytics and technology advancements to perform near real-time subject-level data review and site performance analysis to improve patient safety and improve the overall study quality.

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• RBM is using advanced technologies, including AI, ML, and predictive analytics to provide new levels of insights to mitigate risks while improving quality and patient safety
• Oncology trials are an industry leader in the adoption of RBM practices for their clinical trials — understand why with case studies and lessons learned from this webinar

CONTACT US clinical@iqvia.com
For technical questions about this webinar, please contact Martha Devia at MDevia@mmhgroup.com
Top 5 Global Clinical Trial Disclosure Changes in 2020 Amidst Pandemic

Spotlight on clinical trials created by COVID-19 pandemic has forced regulatory officials around the world to expand disclosure requirements on results.

This year has been a busy one in the clinical trial disclosure and transparency space. The coronavirus pandemic has encouraged the rapid sharing of clinical data at a speed and scope that well exceeds regulatory requirements. It is unclear whether this broader and earlier data availability will eventually impact disclosure regulations, but it is no doubt shaping expectations and redefining what is possible.

On the regulatory front, 2020 has seen five significant developments:

• In the US, a federal district court expanded the results disclosure requirements following a lawsuit brought against the National Institutes of Health (NIH).
• The US Federal Drug Administration (FDA) published guidance on civil monetary penalties related to trial disclosure.
• The European Medicines Agency (EMA) updated its plans for implementing its Clinical Trial Information System (CTIS), the EudraCT replacement system, by the end of 2021, bringing the Clinical Trial Regulation EU No 536/2014 into effect.
• Brexit will change how clinical data are made public for trials conducted in the UK and require substantial organizational and process changes for UK and EU organizations.
• Japan made the disclosure of protocol and trial results information mandatory on the JRCT registry.

Expansion of trial results disclosure requirements in the US

On Feb. 24, the US District Court for the Southern District of New York ruled that results for all trials applicable to the FDA Amendments Act section 801 of 2007 (FDAAA 801) must be disclosed on ClinicalTrials.gov. The disclosure deadline is no later than 30 days after the studied product is approved, licensed, or cleared (approval), even if that approval occurred after trial completion.

Issued in 2016, the Final Rule clarifying and expanding FDAAA 801 had revised the requirements for disclosing results of applicable clinical trials completed before the rule’s enactment on Jan. 18, 2017. Under the Final Rule, results for applicable trials were only required if the product was approved (or the device cleared) for any use before the trial’s completion date. Previously, FDAAA 801 required disclosure of results for applicable clinical trials within 12 months of the completion date or 30 days after the product approval, whichever came later, irrespective of whether the product was approved or cleared before or after the trial completion date. The ruling by the Southern District of New York invalidated the Final Rule results reporting exception for trials of products approved after the completion date.

On July 28, the NIH accepted the ruling, requiring results disclosure of applicable clinical trials studying a drug, biological, or device product approved by FDA within 30 days of the approval. If the disclosure deadline has already passed for trials affected by the ruling, results are due as soon as possible.

FDA final guidance on civil money penalties relating to trial disclosure

The FDA has issued the final guidance related to financial penalties for noncompliance with US trial registration and results disclosure regulations. Following is a summary of the steps the FDA will take in issuing financial penalties for noncompliance with 402(j) of the Public Health Service Act (PHS Act) and 42 CFR part 11:

1. The centers identify a violation through the FDA’s Bioresearch Monitoring Program (BIMO) or based on complaints received by the agency.
Disclosure practices are under considerable scrutiny by transparency advocates and patient groups.

2. The centers will send the responsible party a Preliminary Notice of Noncompliance (Pre-Notice) Letter, which describes the potential violation and requests that the responsible party take any necessary actions to address the possible violation within 30 calendar days of receiving the letter. Failure to comply with the requirements relating to applicable clinical trials may result in further regulatory action by the centers, including the issuance of a Notice of Noncompliance, civil money penalties, injunction and/or criminal.

3. 30 days after issuing a Pre-Notice letter, the centers will follow up on the violation if the submitter fails to submit the required certification to the FDA or knowingly submits a false certification. In that case, the agency intends to issue a Notice of Noncompliance to the submitter, giving the sponsor another 30 days to remediate. The Notification of Noncompliance will be made publicly available on the agency’s website and ClinicalTrials.gov.

4. Failure to remediate the issues identified in the Notification of Noncompliance within 30 days means the centers intend to seek civil money penalties, taking into account the type of noncompliance and the circumstances associated with the lack of remediation.

**Considerations and next steps**

Disclosure practices are under considerable scrutiny by transparency advocates and patient groups. Noncompliant organizations are identified publicly, with their trials listed with the potential fines that the FDA could be collecting. While the final guidance on civil money penalties describes a fairly lenient process where the FDA provides organizations with time to address noncompliance, the public naming and shaming can have serious reputational impacts. Industry sponsors with large portfolios of trials tend to be highly compliant with the disclosure regulations. However, more than 60% of trials conducted by smaller sponsors are noncompliant, creating significant regulatory risks that may affect valuations and create challenges during a future acquisition.

Organizations should conduct an internal disclosure audit of all trials posted to ClinicalTrials.gov to identify potential issues, including trials of acquired products or companies. At a minimum, these trials should be reviewed on the FDAAA TrialsTracker to confirm compliance with the Final Rule, though this will not help assess compliance with the original FDAAA 801.

**EU CTIS**

The EMA has shared its plans for implementing the new CTIS, replacing the current EudraCT system used to submit and manage Clinical Trial Applications (CTAs) and trial results in the EU. The CTIS will support a centralized procedure for submitting CTAs and is now expected to go live in December 2021, provided the independent audit scheduled to start in November 2020 does not uncover significant issues. Six months after the European Commission publishes a notice confirming the full functionality of CTIS following the independent audit, the EU Clinical Trial Regulation (Regulation EU No 536/2014) will go into effect.

**Considerations and next steps**

For the first 12 months after the CTIS go-live, sponsors and investigators may submit new CTAs to either the current EudraCT system or the new CTIS. After the first year, new CTAs must be submitted to the CTIS, and 36 months after go-live, all ongoing trials must be available in the CTIS, including those initially registered in the current EudraCT system.

Since the CTIS will change the processes and data layout for submitting CTAs, and the flow of communication with competent authorities, plans to adjust SOPs, work instructions and stakeholder communication should be in development. While the use of the CTIS is not mandatory for the first 12 months after go-live, it is recommended to identify at least one or two trials to submit through the new system in 2022 to prepare for the mandatory use in early 2023.

**Brexit**

Because the United Kingdom is part of the European Union, protocols and results for trials conducted in the UK were made public on the EMA’s EU CTR. Sponsors initiating trials after the UK exits the EU on Dec. 31, 2020, will be required to register trial protocols and results for interventional trials on alternate public trial registers such as the ISRCTN registry or ClinicalTrials.gov ac-
According to the Make it Public strategy published by the National Health Service (NHS). By the end of 2021, around the time that the EU CTIS system goes live, the UK expects to make a new clinical trial data hub available to support UK patients and researchers.

**Considerations and next steps**

The UK will recognize ethics and regulatory approvals for clinical trials that were granted through the current EU processes before Dec. 31, 2020, but any trial starting after 2020 will need local UK approval.

For trials that are ongoing after Brexit with locations in the EU where the Medicines & Healthcare Products Regulatory Agency (MHRA) is the Reference Member State (RMS), the sponsor will have to find a different Concerned Member State (CMS) to take over the role of the RMS. Also, while trials conducted in the UK after Brexit will be made public on registries other than EU CTR, any trial conducted in the UK that completes by Dec. 31, 2020, will require results posting on EU CTR, even if the disclosure deadline is after Brexit. Although sponsors have options where they chose to disclose UK trials starting Jan. 1, 2021, the recommendation is to use ClinicalTrials.gov as it is the most comprehensive global registry with currently around 360,000 trials publicly available. However, trials that also have locations in EU member states (other than Phase I trials without pediatric participants) will be publicly available on EU CTR.

Following Brexit, sponsors of clinical trials will have to ensure they have established appropriate local representatives in both the UK and the EU, including the Qualified Person for Pharmacovigilance (QPPV), the QP to certify compliant product manufacturing, and a local Market Authorization Holder (MAH). Unless the EU and the UK come to an agreement, sponsors will also need to establish batch control testing sites in both regions.

**Japan Registry of Clinical Trials (jRCT)**

Sponsors and investigators in Japan have had the option to publicly disclose clinical trial information on one of three registries, UMIN CTR, JMCATT CTR, and JapicCTI. Posting trial information on these registries was not mandated by Japanese regulations, though ethics committees, industry associations and organizational commitments may have required registration. However, Ministry of Health, Labor, and Welfare regulations now require the registration of all Phase I-IV interventional clinical trials on the jRCT for studies that started on or after Sept. 1, 2020. The protocol registration is due before the start of enrollment and is submitted in Japanese and English. Sponsors must disclose the results of registered trials within 12 months of study completion. However, it may be possible to delay results disclosure until 12 months after product approval or sale in any country.

**Considerations and next steps**

Industry sponsors that have made their trial data public on JapicCTI in the past must now post their trial information on jRCT instead and recognize the need to register Phase I trials (other than bioequivalence studies) before enrollment starts. The mandatory registration and results disclosure may necessitate updating standard operating procedures (SOPs) as well as agreements with clinical research organizations (CROs) or investigators.

**Summary**

There are over 40 trial registries globally with an average of two new registries starting each year since 2000. These registries make data publicly available for trials run in well over 100 countries, based on a broad range of local regulatory requirements. With increasing public scrutiny and the inspections by national health authorities, organizations conducting multinational trials must have the regulatory intelligence and tracking capabilities to keep up with the evolving requirements. Sponsors may choose to dedicate internal resources to disclosure or outsource this function to vendors with a specialization in disclosure. In either case, 2021 is expected to bring significant additional changes that will require organizational resources and expanded investment in disclosure and transparency.

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1. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH)
2. Disclosure of bioequivalence studies is not required.
Clinical Development of Oncology Products in Japan — the 2nd Largest Market for Innovation

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Japan is the second largest market for branded pharmaceuticals and innovation and continues to show strong year-on-year growth. Continuous investment in development in Japan is creating many opportunities and growing the potential for multinational biopharma companies.

This is driven in part by Oncology. With recent advances in genomic analysis technology, such as next generation sequencing (NGS), progress is being made in establishing genomic cancer medicine, whereby effective therapies are selected based on the results of genomic analysis of each individual patient.

In addition, the Japanese market is driven by ongoing regulatory and government initiatives that reward innovative product development. Such measures include accelerated review systems such as Sakigake and Conditional Early Approval. Other driving factors are related to shifts in population demographics leading to over 1 million cancer incidence in Japan each year.

Join IQVIA Japan as we discuss opportunities within the Japanese Oncology market and how you can take advantage to increase the value of your Oncology assets.

3 Key Takeaways

• To obtain the information about the Oncology market in Japan
• How to seize the opportunity in this strong potential market
• Overview and changes in the Japanese Regulatory Environment and international development strategy

CONTACT US
Japan@iqvia.com

For technical questions about this webinar, please contact Martha Devia at MDevia@mjlifesciences.com
Managing Risks in Clinical Trials During a Pandemic with ICH E6 (R2)

COVID-19 pandemic forces compliance within organizations following FDA’s 2018 revision of Good Clinical Practice in federal registry.

In March 2018, FDA placed ICH E6 (R2), a revision to Good Clinical Practice (GCP), in the federal registry. This regulatory update made explicit the responsibility of the sponsor to understand the risks to quality in clinical trials via the use of a Risk-Based Quality Management (RBQM) approach. Consisting of a variety of required components—including but not limited to quality risk assessments, a written Quality Risk Management Plan, and strategic, centralized data reviews—the revision underscores the importance of a robust RBQM framework to ensure clinical trial execution in compliance with GCP.

In the months since ICH E6 (R2) was adopted, a global pandemic has impacted clinical trial operations. However, even before the pandemic, many companies were still working to become compliant—and while COVID-19 has introduced its share of roadblocks to the industry, it has also prompted sponsors to intentionally embrace the adoption of a RBQM framework to new and ongoing trials.

In this article, we will examine the overall value of ICH E6 (R2) to sponsors, as well as how COVID-19 has and will continue to influence sponsors’ consideration of risk-based monitoring as a key component of clinical trial operations.

Benefits to ICH E6 (R2) and an RBQM framework

Early, targeted risk assessment tells you where you need to look and watch. In other words, to adopt a RBQM framework means to focus more on what matters most: the critical data/processes and potential risks unique to each trial. As the foundation for a targeted, risk-based approach to monitoring, RBQM helps sponsors first identify and understand their trials’ most critical risks before choosing the monitoring strategy that provides the most value.

So, what exactly does ICH E6 (R2) ask of sponsors, and what benefits does it offer in return for the time invested in making the transition? As it currently stands, ICH E6 (R2) requires sponsors to implement the following:

- **Quality risk assessments**, starting at protocol development and ending with database lock
- **A written RBQM Plan and demonstration of plan execution**
- **Strategic data reviews throughout the clinical trial**
- **A robust RBQM framework and approach to ensure regulatory compliance**

While these additional assessments and reviews may seem overwhelming at first glance, it is important to consider these requirements alongside the benefits they provide:

- Improves the likelihood of a high-quality clinical trial
- Ensures clinical trial execution in compliance with GCP
- Focuses on data and risks critical to trial endpoints and patient safety
- Provides quick access to data insights across clinical sites and patients
- Potentially reduces the amount of on-site monitoring needed

The risks of foregoing an RBQM framework

In efforts to adapt the ICH E6 (R2) revision, many companies have encountered difficulty transitioning to a risk-based approach and adaptive monitoring strategy. However, the potential risks that could result from foregoing an RBQM framework far outweigh the transitional period.

For sponsors still weighing the necessity of adopting a RBQM approach, it is important to recognize that the decision to skip proactive, risk-based monitoring brings a risk to safety, data integrity, and even primary endpoints, any of which could drastically impact trials if not monitored appropriately.

Likewise, clinical trials characteristically produce massive amounts of data for study staff to sift through. However, if they have not proactively identified key data and processes that could bring potential risk, they run the danger of getting “lost in the weeds” and overlooking risk factors that later breached tolerance limits and resulted in issues that had some level of impact on the study and its results.

Employing the expertise of a CRO is an option for sponsors to help alleviate the work and time
commitment required to adopt a RBQM process on their own. At Rho, we consider a robust RBQM framework to include dedicated quality risk managers, RBQM templates to assist with creating the plans required by ICH E6 (R2), a strategic approach to data review, among other components.

COVID-19, ICH E6 (R2) and a risk-based future

The global pandemic is a major risk in and of itself, and it has certainly revealed the extent of its negative impact on a variety of industries, resulting in closures, layoffs and more. When observed through a clinical research lens, COVID-19 is the type of risk that should be accounted for proactively—ideally via an RBQM approach. However, the reality is the shocking and surprising onset of the pandemic did not provide the clinical research industry—or any industry—the foresight to prepare for every single roadblock presented by a pandemic of this scale.

For many ongoing clinical trials, when the pandemic hit, sites stopped seeing patients in-person, encountered issues with enrollment, along with other delays. This required sponsors to pause and identify what risks COVID-19 could bring about to potentially impact the future of the trial. Arguably, this situation has forced sponsors to look at their trials through an RBQM lens and adopt this process or encounter the risk of halting their trials altogether.

On the other hand, those in the planning phase have the privilege of incorporating pandemic-related mitigations into their programs up front.

During this stage, an early adoption of RBQM provides the opportunity to proactively determine what can be monitored centrally or conducted remotely via an on-site visit or very limited on-site visits to safeguard patient and staff health and safety.

Overall, ICH E6 (R2) underscores the sponsor’s responsibility to evaluate and implement risk-based monitoring into their clinical trials, before, during and even after the era of COVID-19. We consider a risk-based future to consist of the following:

- Site monitoring visits conducted based on tracking and managing risk at the site
- Initial set of visits may be pre-planned but then visits are driven by findings—leading to a variable frequency of visits across the study and between sites
- More findings or more severe findings leads to more visits and vice versa
- Visit types (off- or on-site) driven by number, severity, and type of findings

It is important to note that the possibility of more on-site visits will likely be delayed as we continue to adapt and recover from the impacts of COVID-19. However, decentralized clinical trials provide a viable solution for this setback, as long as they are patient-centric, customized and rooted in a robust RBQM framework, per the ICH E6 (R2) guidance.

Conclusion

Arguably, the global pandemic has redefined our understanding of a “traditional” clinical trial, as more sponsors are implementing decentralized clinical trials to keep studies active during this time. Despite this shift, many organizations have still been slow to adopt ICH E6 (R2) and make the necessary updates. Future updates to ICH E6 (R2) will likely be driven by this need for more frequent adoption of the revisions, as well as pave the way for an easier industry-wide transition to a risk-based monitoring approach.

E6 (R3) on Horizon

As the new calendar year approaches, organizations are beginning to look forward to understanding the impact of ICH E6 (R3) in the fourth quarter of 2021. Despite E6 (R2) being released just four years ago, the industry is still facing difficulties in adhering to these current regulations.

A webcast presented by Applied Clinical Trials and sponsored by Oracle Health Sciences in late summer addressed what organizations can do to prepare for E6 (R3) [see: https://bit.ly/2kOdQj6]. The webcast featured insights from three industry leaders; Crissy MacDonald, PhD, Executive Director, Client Delivery, The Avoca Group; Andy Lawton, Consultant, Risk Based Approach Ltd, and Elvin Thalund, Director, Industry Strategy, Oracle Health Sciences.

E6 was originally released in 1996, creating the first guidance for clinical trial context. In 2016, revisions were made to these regulations for the first time in 20 years, forcing an industry-wide shift as it attempted to adjust. With another update to E6 expected in 2021, there will be a gap of just five years between revisions.

“What we’re seeing is a shrinking timeline of these regulatory guidance revisions, and it’s likely related to the rapid changes in technology’s clinical trial design approaches,” said MacDonald. “We need to become more adept at adjusting our internal policies and procedures to comply with these newly changing regulations.”

Lawton highlighted the revisions to E6, as well as the latest revisions to ICH E8, that will encourage greater use of quality tolerance limits (QTLs). “Quality tolerance limits give us that one perfect gift of avoiding perfection, because we write our plans as if we’re going to achieve perfection,” he said. “We can move away from that definition of perfection to a defined quality basis.”

Currently, organizations use a trial-reporting system that includes a completely separate process for quality checks after the fact. “There’s currently a whole secondary process, in this case a TMF (trial master file) process, where now the true regulatory quality is being assessed. The solution could be a system which considers quality from the very beginning. It would include training operational staff members on ICH regulations and implementing quality checks early in the process,” Thalund said.

“When you then start receiving them (documents), you can now ensure your quality control based on the quality you had defined from the beginning,” Thalund said. “That’s where you now have quality by design built into your system and process.”

The E6 (R3) concept paper states that R3 will be a full rewrite and reorganization of the GCP (good clinical practice) guidance with a focus on the applications of GCP principle to the increasingly diverse trial types and retaining concepts already present in R2.

While MacDonald noted the industry’s tendency to have a reactive approach to new regulations, when it should be more proactive, “[the industry’s] reactive approach has driven a decrease in adoption because there’s concerns without a clear understanding of what those regulatory expectations are,” she said.

To address this, MacDonald referred to the Pharmaceuticals and Medical Devices Agency (PMDA)’s idea of “horizon scanning.” This concept will consist of “scanning the horizon” to find emerging technologies in order to proactively prepare and make the necessary regulations a priority.

Although the ICH E6 (R3) revision is fast approaching, models such as horizon scanning and streamlined operational processes should be able to help organizations adjust to the newest set of regulations.

—Andy Studnu is an Assistant Editor for Applied Clinical Trials
With COVID-19 vaccines set to take center stage in the coming months, recent study compares late-stage COVID vaccine trial sites with historical placement practices.

Late-stage COVID-19 trial placement

Overall, we found that approximately half (53%) of OWS clinical trials are placed within site networks; one-third (34%) of clinical trials are placed within academic medical centers; 5% within health systems; and the remaining 8% are roughly evenly placed within government entities and independent medical practices.

With the exception of Janssen’s late stage COVID-19 clinical trials, site networks and academic medical centers operating in the US were the dominant two settings. SNs and AMCs combined to account for almost 90% of all clinical trial settings for AZ, Pfizer and Moderna programs; these two segments together account for 75% of sites conducting the Janssen clinical trial. For-profit site networks were the largest category in every clinical trial except for those sponsored by AstraZeneca, where AMCs comprised the majority.

Site networks made up at least two-thirds of both Moderna and Pfizer’s study sites; whereas they only accounted for about 40% of sites in Janssen and AstraZeneca’s clinical trials. The similar site placement patterns observed in Moderna and Pfizer’s clinical trials may in part be due to their use of the same contract research organization (PPD).

Academic medical centers account for over half of AstraZeneca’s sites (52%), making them the only sponsors to have engaged more AMCs than SNs.

Janssen has almost five times as many government entities as the next closest sponsor with 10%
of all clinical trials being placed within federally-funded institutions. This is in part due to Janssen and BARDA’s higher relative utilization of Veterans Affairs offices.

Janssen’s COVID-19 clinical trial is the most evenly dispersed across for-profit and not-for-profit organizations. Moderna and Pfizer are the most heavily weighted toward for-profit investigative site settings (68%-70%) vs. not-for-profit settings (24%-28%).

Comparing COVID-19 trial placement to past placement practice
The most striking observation in this study is the remarkable consistency of placement practices over time including those testing new treatments and vaccines for COVID-19. In 2013, a study from the Tufts Center for the Study of Drug Development (CSDD) noted that “53% of all global FDA-regulated clinical trials are now conducted by independent, community-based principal investigators”.1 This 53% share of the total site landscape is identical to the share captured by site networks in COVID-19 vaccine trials.

Academic medical centers have held on to a more modest share of industry-funded clinical trials. In a 2007 report, Tufts CSDD noted that “today, only one-third of all industry-funded clinical trials are placed within academic clinical trials offices”.2 Our study found a similar percentage —34%—of late stage COVID-19 vaccine clinical trials are being conducted within academic settings.

Academic medical centers have not been alone in their inability to increase market share of industry-funded clinical trials. Government entities—such as Veterans Affairs offices—have captured an even smaller share of this market. This is due in part to the protracted contracting, negotiations, and bureaucracy that historically contribute to slower study start-up times there when compared to that of site networks and dedicated investigative sites.3 Academic medical centers have leveraged their experience, prestige, infrastructure, and patient volume to maintain their market share. The VA setting, on the other hand, has been a consistently less attractive place for industry-funded trials.4 During the pandemic, with increased interest in public-private collaboration, the VA setting for industry-funded clinical trials will likely receive greater visibility.

Comparing sponsors of late stage COVID trials, those companies most closely collaborating with government and non-profit partners (e.g., AstraZeneca and Janssen) have placed their clinical trials in a higher relative percentage of academic medical centers. In the case of AstraZeneca, this decision is consistent with the company’s historical site placement practice: In 2007 AstraZeneca’s R&D director Ellis Wilson remarked that, “by mitigating bottlenecks on the critical path, academic sites are becoming more attractive and may even start to account for a growing proportion of trial placements. The pendulum is swinging back in their direction. And pharmaceutical companies want to be their partner of choice”.5

Discussion
In the past, sponsors have relied on independent, for-profit investigative sites when speed and efficiency are paramount. In today’s COVID-19 vaccine landscape, the same holds true. Moderna and Pfizer’s studies, with their heavy reliance on for-profit sites, are moving the fastest in the race to prove the safety and efficacy of their vaccines.

Given the consistency observed in investigative site placement practices, we can assume that there will be a similar consistency in sponsor experience with participant diversity and inclusion for their COVID-19 trials. We can expect to see the same levels of proportional representation by participant demographic subgroup: White and Asian participants will be overrepresented, and participants from minority communities—most notably those of Black and African descent—will be underrepresented. This is particularly concerning given the higher observed rate and severity of COVID-19 cases among minority communities. Indeed, a lack of diversity has already been documented in both the NIAID Adaptive COVID-19 Treatment Trial (ACTT-1) and the Gilead-funded remdesivir study.6

It is interesting to note the very low percentage of investigative sites from health systems and independent medical centers participating in these late stage COVID-19 clinical trials. Although these segments offer access to a large volume of patients within clinical care settings, combined they account for less than 10% of total sites. Similar to pre-pandemic conditions, these entities have been less attractive settings when compared to site networks and academic medical centers that offer
larger numbers and more dedicated personnel; higher levels of experience and competency; and substantially greater research infrastructure. Hospitals and independent medical centers were also the slowest to respond during the early stages of lockdowns throughout the US, and these sites were among the most likely to suspend their clinical trials at the outset of the pandemic.\(^6\)

Community hospitals often find themselves being passed over during site selection in favor of academic medical centers which boast experienced investigators and specialized researchers.\(^7\) This is another reason why new investigators and health systems are not participating in COVID-19 clinical trials: sponsors place a high value on prior experience rather than total potential for accessing and attracting a large and diverse patient population. This fact makes it difficult for new investigators and sites to get their foot in the door for new clinical trials, and nowhere is this trend reflected more than in this research. Sponsors and CROs are choosing to place their study sites within entities that have proven track records, and the result is that site networks and AMCs account for over 85% of late stage COVID-19 vaccine trial sites.

Some independent medical practices and health systems are turning to partnership as a way to win and participate in more trials. The integrated research organization (IRO) is an emerging model that is allowing multi-specialty practices and community health systems to be involved in clinical trials as a research care option for their patients. Privia Health, Tryon Medical Partners in Charlotte, North Carolina, and the AMC of Wake Forest University Health, for example, are benefitting through partnership with IRO Javara Research to participate in COVID-19 vaccine trials which other health systems in the same geographic areas in some cases have not managed to secure. We can expect to see these integrated research partnerships become more common as other health systems and medical practices recognize the high-profile COVID-19 studies that IRO partners have been able to win.

In the race against time, during a pandemic that has, to date, claimed nearly 250,000 lives, sponsors and CROs are placing their COVID-19 clinical trials in the same places that they have been doing so for decades. Site networks and academic medical centers continue to dominate— and the majority are based in the US. Independent medical practices, health systems, and government entities are playing a relatively small role in late stage COVID-19 clinical trials. Sponsor company site placement practices may likely contribute to participant disparities by race and ethnicity typically seen in pre-pandemic clinical trials unless remedial and innovative approaches are utilized.

References
The Patient Voice in Rare Disease Research

Listening to patients and families is more important than ever

On-demand webinar
Aired October 22, 2020

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In rare disease research, patients and families are taking a seat at the table, providing real-life perspectives that are helping to shape the development of new therapies. Sponsors, regulatory agencies, payers and health care providers alike are seeing the value of this increasing patient involvement.

In this webinar, IQVIA and the Rare Disease Innovations Institute bring together different voices from patients, families and other stakeholders to highlight the importance of the patient voice in rare disease development — now and in the future.

Learn how rare disease patients and families have been impacted by the pandemic, and why listening to their voice now is more important than ever. Register now!

3 Key Takeaways

- Recognize the value of including the rare disease patient’s perspective in clinical research
- Understand the impact of COVID-19 pandemic on rare disease patients and families
- Discover new ways to make clinical trials more patient centric

 MODERATORS
Tara Britt, Founder and President, Rare Disease Innovations Institute, IQVIA
Ali Smyth, PhD, Strategy Director, Pediatric and Rare Disease Center of Excellence, IQVIA

PATIENT ADVOCATES
Jenny Klein, Research Scientist, Collaborations Pharmaceuticals
Parvathy Krishnan, Director of Patient Engagement, Rare Disease Innovations Institute, IQVIA
Justina Williams, Patient Engagement Coordinator, Piedmont Health Services and Sickle Cell Agency

SPEAKERS
Cindy Powell, MD, Professor of Pediatrics and Genetics, University of North Carolina at Chapel Hill
Jeff Keefer, MD, PhD, Global Head, Pediatric and Rare Disease Center of Excellence, IQVIA
Mike Zincone, Sr. Director, Public Affairs Rare Disease, Pfizer

Presented by:

Sponsored by:

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Gender Bias in the Clinical Evaluation of Effectiveness in Therapies

Past decades have shown gender-based differences in clinical trial results are often overlooked when considering safety and effectiveness.

It is increasingly apparent that many physiological and pathological functions as well as patterns in gene expression differ between women and men and gender differences have also manifested in the outcomes of treatments. Throughout the last decades, alarming evidence of gender-based differences in the safety profiles of treatments has accumulated. A study including 513,608 patients estimated that women experience a 1.5 to 1.7-time greater risk of developing adverse reactions to drugs than men. In 2001, a report from the U.S. General Accounting Office (GAO) made the observation that 70% of drugs withdrawn from the market between 1997 and 2000 presented greater health risks for women.3 On top of that is data suggesting that women are overdosed: the dose of zolpidem, for example, was reduced by 50% in women, after studies showed that women have five times more risk than men of driving impairment after 10 mg of zolpidem.4 Gender differences have also been spotted in effectiveness of treatments: 20 years after the Physician’s Health Study (a clinical trial that excluded women), a large placebo-controlled primary-prevention trial involving 39,876 women demonstrated that daily low dose aspirin has no significant efficacy on the risk of myocardial infarction or death from cardiovascular causes in women, as opposed to results in men.5

These differences in the outcomes of treatment can be explained by well-studied gender differences in all the phases of pharmacokinetics and the growing literature in pharmacodynamics describing gender differences in drug-receptor affinity, receptor density, or signal transduction pathways. Despite these evidences, gender is still one of the most underappreciated variables in the clinical development of drugs. To address this shortcoming, it is important to clearly define the place of clinical trials in identifying gender differences.

Enrolling an appropriate number of women

Since the thalidomide disaster of the 60s, it became a common practice to protect fetuses from clinical trials, rather than protecting them through well controlled clinical studies. In 1977, the FDA excluded “women of child-bearing potential” from Phase I and early Phase II clinical research. This 1977 FDA guideline was, however, applied to all pharmaceutical research and the expression “woman of childbearing potential” was defined too extensively as any woman capable of becoming pregnant, regardless of their sexual activity, their use of contraceptives, their sexual orientation, the possible sterility of their partners, or even their desire to have a child. Additionally, several publications indicated that teratogenicity can also be transmitted via sperm. This dangerous ban was in application until 1993 and countless drugs were put on the market through clinical research that underrepresented women, exposing (until this day) women to drugs that were not or less tested on them. The FDA 1993 guidance reversed the ban and recommended that clinical studies include men and women “in numbers appropriate to allow the detection of clinically significant gender differences in drug responses.”

This raises several questions: Firstly, what is an appropriate enrollment of women? Gender bias is a complex problem and will not necessarily be solved by the simple achievement of a 50:50 distribution of participants’ gender. Rather than considering only rates of enrollment, a participation to prevalence ratio (PPR) superior to 0.8 is an indicator of appropriate enrollment of women and addresses gender differences in disease prevalence. In the beginning of the new millennium, the GAO suggested that women are “sufficiently represented in clinical trials” but several authors disagree. Regarding late phase clinical trials, Pool et al. estimated in 2009 that the participation...
of women between 2007 and 2009 was 43.3%, and 3.5% of the clinical trials still unspecify the sex.22 In 2020, Jin et al. revealed that among 740 cardiovascular trials conducted between 2010 and 2017, only 38.2% of participants were women. Furthermore, a participation to prevalence ratio inferior to 0.8 was associated with arrhythmia, coronary heart disease, acute coronary syndrome, and heart failure trials.23

Secondly, how early in drug development should enrollment of women be a concern? Pinto et al. estimate that only 30.6% of Phase I trial participants are women and 34.1% of early trials enroll exclusively men.24 These findings indicate that all the data imminent from early clinical trials, including dose tolerability, dose and use of a drug, the metabolic and pharmacologic data, side effects associated with increasing doses and even the choice of the investigational drug tested in large-scale trials, are mainly tailored based on data from men. Still, is Phase I early enough to worry about avoiding gender bias? Most of our fundamental knowledge of drugs comes from non-human models including animals, tissues, and cell lines, but about 80% of non-clinical studies use only male animals.25 The differences in drug response between female and male animals could forecast the differences in treatment outcomes between women and men patients. In cardiotoxicity studies of dofetilide in rabbit, 100% of female rabbits vs. 30% of males developed severe cardiac arrhythmias and female rabbits developed cardiac arrhythmias at doses 50% lower than those given to males.26 This can be explained by the protective action of testosterone through shortening of the baseline QT intervals.27 Since women are more sensitive to QT interval prolongation than men,28 testing drugs on male-only animals could lead to widely under-estimate cardiotoxicity.

**Gender-based analyses**

Even if the rate of enrollment of women is appropriate, pooling data of both genders may still yield inexact results and problems of reproducibility. Several theoretical models and clinical trials have demonstrated that pooling data from women and men can mask important male and female differences in baseline data, treatment response and also in sex treatment interactions and leads to biased results that are not adapted to women, nor are they rigorously adapted to men either.29

The Digitalis Investigation Group clinical trial is a prime example of the complexity of subgroup analysis. In 1997, the results of the digoxin trial were published, and the outcome was positive. In 2002, Rathore et al. obtained a public-use copy of the data base of the Digitalis Investigation Group and conducted the same study again but performing an analysis based on gender, and the results were alarming. The results for men were identical to the original results, but in women, it was found that digoxin significantly increased mortality and digoxin-associated reduction in the rate of hospitalization for heart failure was smaller.30 The results of this post-hoc analysis were not reproducible in large observational studies.31,32 When gender-based analysis of randomized controlled trials (RCT) and observational studies are inconsistent, it may raise some confusion. On one hand, post hoc analysis of RCT have less statistical power to detect an interaction between gender and effectiveness of treatment, and even less power to detect interaction between gender and uncommon adverse events and are more prone to type 1 errors (false positive) to detect interaction. On the other hand, observational studies are not randomized, and are biased by unmeasured confounders that affect the interaction analysis. To reduce the weaknesses in the observational design in this regard, propensity-matched analysis reduced the bias due to confounding variables that could be found in an estimate of the treatment effect. To avoid overinterpretation, gender-based analysis must thus be performed but in very strict conditions:

1. Ensure that there are sufficient numbers of subjects in both gender subgroups.
2. Provide a rationale for performing the subgroup analysis.
3. Perform a statistical test of interaction between gender subgroups is necessary but not sufficient.
4. Adjust p-values for the number of comparisons being made.
5. Emphasize overall findings: results of gender-based analyses should only be used to produce hypothesis that should be confirmed through post marketing (larger scale) studies.

In 2007, it was reported that among RCT performing a gender-based subgroup analysis, only 35% of studies performed a proper subgroup analysis.33

Gender bias is a complex problem and will not necessarily be solved by the simple achievement of a 50:50 distribution of participants’ gender.
Regarding the sample size, including women and men analysis does not necessarily imply to double of the number of patients to maintain statistical power. More efficient designs, including factorial design (in which two experimental factors with multiple levels are tested, and data are collected across all possible combinations of factors and levels) allow to maintain power at low cost, by increasing the sample size by only 14% to 33%.

**Conclusion**

In 2020, it is estimated that more than 300,000 clinical trials start every year. This represents therapeutic opportunities but also potential harm for subgroups that are not well represented in clinical trials. In order to be reliable and useful, clinical trials need to be both internally and externally valid. Lack of external validity has created a call for more pragmatic “real life data” trials and the production of data that are applicable to all categories of patients. During this era of personalized medicine, “one-size-fits-all” is not acceptable anymore. Patients need a treatment that is well suited for different subgroups, and women and men are different. Sex is a fundamental variable that should be used to disaggregate data and explain differences in treatments outcomes. To avoid this bias, two main criteria are determinant: inclusion of women in the right number and correct gender-based analysis. In late phase clinical trials, there has been improvement, but men still predominate. In 1993, when the ban of exclusion of women in clinical trials was lifted, one on the main concerns was the underrepresentation of women in cardiovascular trials. In February 2020, the same concern is still raised concerning drug trials on cardiovascular diseases, the leading cause of death. In early phases of clinical trials, women are still largely underrepresented or even excluded, fostering a gender bias in the data of dose tolerability, appropriate dosing, metabolic, and clinical pharmacology. Moreover, when research lacks or excludes female subjects, the guidelines should clearly state that the evidence has been obtained mainly from men. Once a drug is marketed, the scientific or patient leaflet should mention the ratio and total number of women and men that participated in the clinical trials. Regarding analyses by subgroup, it is estimated that only half of clinical trials perform gender-based analysis and only 35% conduct proper subgroup analyses. Investigators should follow guidelines to ensure the proper conduct of subgroup analysis to prevent misleading conclusions from becoming adopted by clinicians. Overall, inclusion of women and gender-based analysis must continue to improve to ensure external validity, reduce gender bias, avoid distrust in controlled clinical trials, and protect women’s health from drugs that are less adapted to them.

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Radiomics: What It Can Do for Clinical Trials

Radiomics is a new, emerging field of technology that can help life sciences companies discover more about medical images, enabling them to conduct clinical trials with more accuracy and speed while driving greater personalization of treatment. This emerging yet robust approach to imaging analytics extracts meaningful information by discerning vast amounts of radiomic data points from digital images, curates and annotates it, then analyzes the quantitative imaging data to deliver a wealth of information. Radiomics unleashes powerful insights about the characteristics and progress of lesions and tumors that are not discernible from traditional reading methods of imaging modalities such as CT, MRI, or PET scans so life sciences organizations can leverage them in new ways. Further, this novel set of imaging pattern data enables the discovery of imaging biomarkers which have been proven to be both predictive and prognostic regarding clinical outcomes and treatment pathways.

In healthcare, not all data are created equal. Despite the popular focus on electronic health records, some observers may be surprised to know that approximately 90% of healthcare data is concentrated in just one sector—medical imaging—and 97% of that goes unused or unanalyzed. Traditionally, when clinical or research radiologists have reviewed images of lesions or tumors to determine the effectiveness of a pharmaceutical or other treatment, their view has been limited to two dimensions—length and width. The reality is that lesions and tumors have multiple dimensions, along with thousands of other structural features that define them. Human cancers in particular exhibit strong phenotypic differences that can be visualized noninvasively by medical imaging. Gaining this view, however, requires seeing below the line, and that’s where radiomics enters the picture.

At its foundation, radiomics starts by building an artificial-intelligence-enabled model based on thousands of healthy organ images. The algorithms ingest thousands of variations from that model that show lesions, tumors, their progress, and outcomes. As a result, rather than being limited to looking simply at length and width, these AI-driven analytics can use this information to extract unseen data from the digital image to measure and determine depth, volume, density, doubling size, tumor textures and other features that cannot be observed optically in an image. These analytics not only deliver a view that formerly could only be achieved through invasive surgery such as biopsies; they also provide information about lesion changes that have never been available by any means.

Additionally, the deep learning capabilities inherent in radiomics enable the system to improve itself as more images are ingested and analyzed and more outcomes are confirmed—regardless of the type of lesion. Over time, the system can track the progression or regression of lesions more accurately to determine the effectiveness of the treatment, providing new insights to life sciences organizations to leverage in therapeutic pipeline decisioning, such as accelerating or ending drug development based on treatment efficacy.

Radiomics’ ability to extract data from digital images and show what would otherwise be unseen can be used by life sciences organizations in clinical trials in the following three essential ways:

Accelerate therapy development
Radiomics can help accelerate therapy development and clinical trials by enabling researchers to compare sequential images to determine how a lesion has changed, indicating whether the drug is effective, why it is effective, to what degree it is effective, and how long it takes to achieve that effect. This information can be gathered in real-time during the trial rather than waiting until it is completed (as typically occurs) to enable the life sciences organization to adapt the trial design based on radiomic features and imagining biomarkers.

Enable greater personalization
Radiomics can contribute value in delivering the last mile in personalized medicine. The combination of genomic data, plus the type of phenotypic data radiomics derives from images, provides even greater adaptability to clinical trials by immediately mapping the effectiveness of drugs, showing whether treatments under trial are more effective for patients with shared characteristics.

Discover new biomarkers
In the long-term, radiomics can be used to discover imaging biomarkers to aid in clinical decision-making and treatment. Once developed, life sciences organizations can leverage these biomarkers in clinical trials to inform and manage patient recruitment, assignment to trial arms, and cohort design, such as inclusion criteria and stratification.

More than any other technology, radiomics can help life sciences companies realize the full value of their imaging pipelines.
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