appliedclinicaltrialsonline.com

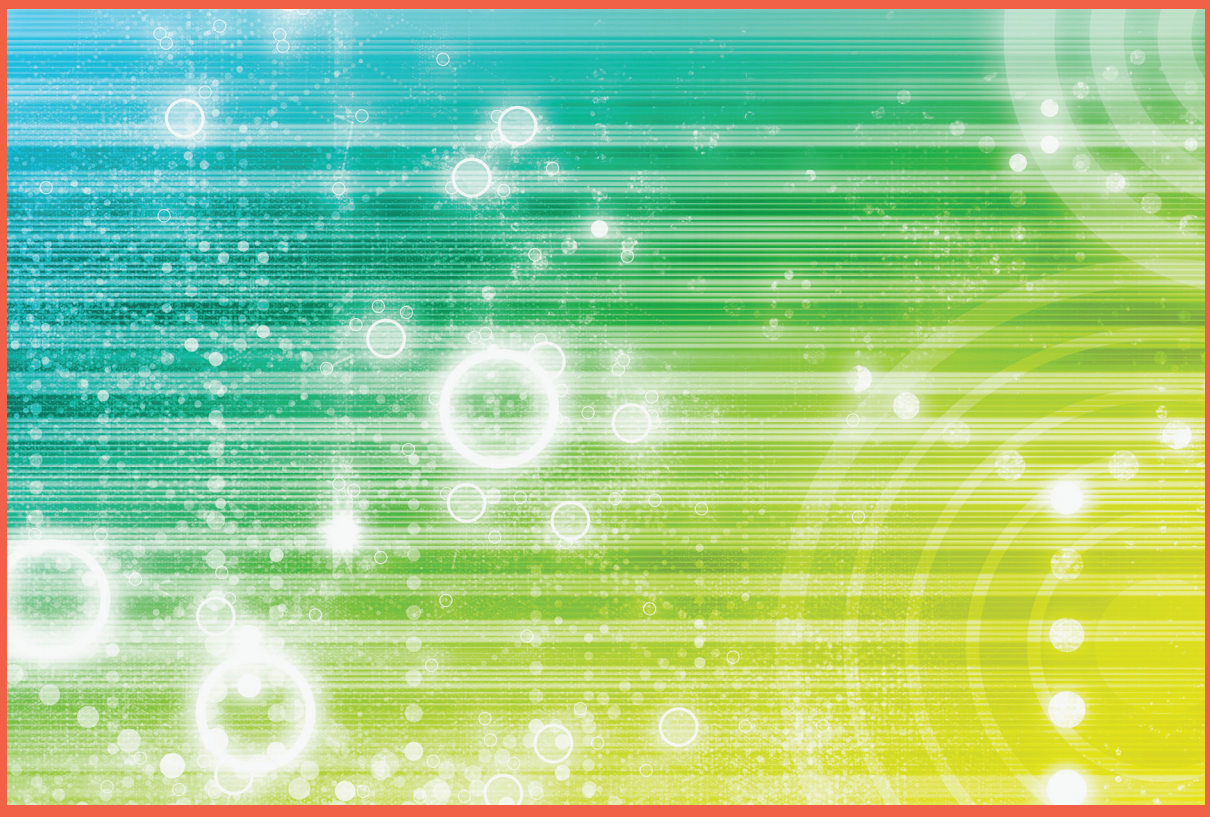
Volume 27 Number 6 June 2018

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

1992–2018 ACT 26th Year of Service

CLINICAL TRIAL DESIGN MODELS IN RARE DISEASE



TRIAL DESIGN

ANTIBODY PK KEYS

PATIENT ENGAGEMENT

PATIENTS AS PARTNERS

UBM

$12

EU REPORT
Policy and Practice Converge on Vaccine R&D

TRIAL INSIGHTS
The Need for New Paradigm in Clinical Study Execution

CLOSING THOUGHT
Why Any Cancer Can Be a 'Rare Cancer'

ADVARRA
advancing better research

MAKE YOUR RESEARCH
altogether better

VISIT US AT **DIA IN BOOTH 1300** TO LEARN MORE!



Integrated Research Compliance Solutions to Streamline Your Study

Advarra is your partner in advancing better research. With an extraordinary breadth and depth of regulatory compliance and human subject protection expertise, a client-centric service model and innovative technology, Advarra provides convenient solutions performed with exceptional quality.

Expert Guidance | Uncompromising Integrity | Rapid Turnaround

IRB Services

IBC Services

Consulting Services

Association for the Accreditation of Human Research Protection Programs, Inc.
Full Accreditation

Trust Advarra's integrated solutions and collaborative approach to make your research **altogether better.**

Get started at ADVARRA.COM >

Hope. The Power for the Rare Disease Journey

LISA HENDERSON
Editor-in-Chief

Unfortunately, there is no end to the number of people affected by disease—be they rare, unmet therapeutic needs, or chronic but manageable. But, everyday, scientists uncover yet another gene, or biomarker, or mechanism of action that leads to the next step in uncovering the true nature of a specific disease, and getting us one step closer to a healthier, longer, or higher quality life.

In addition to advancements in science, are the advancements in drug testing. In this issue, we unveil the results of our trial design survey, conducted with our research partner SCORR Marketing. In that survey (see page 16), respondents shared the types of innovative or flexible trial designs being implemented, primarily but not limited to oncology and rare diseases. By using adaptive or innovative trials, sponsors can theoretically deliver more efficient and faster trials. The FDA and EMA, and other regulatory authorities play a big part in getting rare or orphan drugs through the review process. Starting with scientific advice before a trial is initiated, then offering priority review or other incentives to help sponsors get to the finish line faster.

Children and diagnosis

I wanted to share two recent examples about rare disease in children. The first was my research and interviews with BioMarin for its drug Brineura, approved in April 2017, for the treatment of a specific form of Battan's disease, CLN2. I wrote about it for *Pharmaceutical Executive* here: http://www.pharmexec.com/brands-year-promise-and-challenge, and I encourage you to watch the documentary BioMarin posted on YouTube at http://bit.ly/2kR2OR2.

With Battan, children develop normally until ages two or three, when they experience seizures and progress rapidly to losing the ability to walk and talk by six years of age. After that, symptoms are followed by dementia and blindness; feeding and everyday needs become extremely difficult, and then death occurs between the ages of eight and 12. The video outlines in detail what BioMarin and scientists achieved to get a protein-replacement therapy approved, using one trial of 24 patients with a natural history cohort completed in four years. The drug has only shown to halt the progression, but BioMarin works with commercial lab Invitae to offer a 125-gene panel tests for different types of seizures free of charge. It not only helps diagnose what type of epilepsy may be present, but also diagnose CLN2 in those that were previously undiagnosed.

At the recent Pop-Up Star event, which highlighted programs to increase clinical research awareness, parent Allison Greiner spoke of her son's journey to date with Duchenne Muscular Dystrophy. After observing his lack of hitting developmental milestones, Matthew was enrolled in physical therapy classes, routine medical exams, and more until his diagnosis almost 16 months later. The first clinical trial ended for lack of efficacy, but now he is enrolled in a Pfizer trial and showing tremendous improvement. Greiner is sure that Matthew will continue to thrive and outlast the expected disease timeline of death in the late 20s, early 30s. Greiner said clinical research offer the hope that these parents and patients need.

EDITORIAL OFFICES

485 Route 1 South, Building F, Second Floor,
Iselin, NJ 08830 USA
+1 (732) 346-3080 fax: +1 (732) 647-1235,
www.appliedclinicaltrialsonline.com

EDITOR-IN-CHIEF Lisa Henderson,
lisa.henderson@ubm.com

MANAGING EDITOR Michael Christel,
michael.christel@ubm.com

ASSOCIATE EDITOR Christen Harm,
christen.harm@ubm.com

COMMUNITY MANAGER Lisa Higgins,
lisa.higgins@ubm.com

ART DIRECTOR Dan Ward,
Dward@hcl.com

WASHINGTON EDITOR Jill Wechsler
+1 (301) 656-4634 fax: +1 (301) 718-4377

SALES OFFICES

GROUP PUBLISHER Todd Baker

485 Route 1 South, Building F, Second Floor,
Iselin, NJ 08830 USA

+1 (732) 346-3002. fax: +1 (732) 647-1235,
todd.baker@ubm.com

DIRECTOR OF ADVERTISING Wayne K. Blow

UK: +44 1244 629 304 fax: +44 1925 732 798,
wayne.blow@ubm.com

NATIONAL SALES MANAGER Bill Campbell
+1 (847) 283-0129 fax: +1 (847) 282-1456,
william.campbell@ubm.com

SALES SUPPORT COORDINATOR Kristi Stevenson
+1 (732) 346-3006 fax: +1 (732) 596-0012,
kristi.stevenson@ubm.com

ACT CHESTER UK OFFICE: +44 1244 393 100

MARKETING SERVICES

AUDIENCE DEVELOPMENT MANAGER, C.A.S.T. DATA AND LIST INFORMATION
Melissa Stillwell
(218) 740-6831, melissa.stillwell@ubm.com

PERMISSIONS/INTERNATIONAL LICENSING
Jillyn Frommer
+1 (732) 346-3007 fax: +1 (732) 647-1101,
Jillyn.Frommer@ubm.com

REPRINTS Licensing and Reuse of Content: Contact our official partner, Wright's Media, about available usages, license fees, and award seal artwork at Advanstar@wrightsmedia.com for more information. Please note that Wright's Media is the only authorized company that we've partnered with for Advanstar UBM materials.

SUBSCRIPTIONS +1 (888) 527-7008 (toll-free within USA) +1 (218) 740-6477 (outside USA),
fulfill@superfill.com

BACK OR CURRENT ISSUES +1 (800) 598-6008,
+1 (218) 740-6480 (outside USA)

PRODUCTION OFFICES

PRODUCTION MANAGER Karen Lenzen
Advanstar Communications, 131 W. 1st Street,
Duluth, MN 55802 USA
+1 (218) 740-6371 fax: +1 (408) 962-1125

APPLIED CLINICAL TRIALS (Print ISSN: 1064-8542, Digital ISSN: 2150-623X) is published 4 times/year in March, June, Sept & Dec by UBM LLC 131 West 1st Street, Duluth, MN 55802-2065. Subscription rates: $70 for 1 year (4 issues), $120 for 2 years (8 issues) in the United States and possessions; $90 for 1 year, $140 for 2 years in Canada and Mexico; all other countries $130 for 1 year, $235 for 2 years. Single copies (prepaid only): $23 in the United States and possessions; $28 in all other countries. Add $6.50 per order for shipping and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to APPLIED CLINICAL TRIALS, P.O. Box 6115, Duluth, MN 55806-6115. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A. Digital-only editions will publish 6 times/year in Jan/Feb, April, May, July/Aug, Oct, and Nov.

APPLIED CLINICAL TRIALS
VOLUME 27, NUMBER 6

KENTOH/SHUTTERSTOCK.COM

PEER REVIEWED

24 Monoclonal Antibodies: Clinical Pharmacology Keys

Narine Baririan, PharmD

Outlining the unique pharmacokinetic factors that should be considered when designing and running early stage clinical trials for monoclonal antibodies.

Out of sight, out of mind.

Capsugel® | Lonza Pharma & Biotech

Capsugel®

DBcaps® capsules

Eliminate patient bias in double blind clinical trials and ensure highest patient compliance

Support 90% of marketed oral solid dosage forms

Tamper-evident design

SCAN ME

Made better. By science.

Want to know more?
Visit www.capsugel.com

WASHINGTON REPORT

PATIENT EXPERIENCE MOVES TO CENTER STAGE IN MEDICAL PRODUCT DEVELOPMENT

The Patient-Focused Drug Development (PFDD) program at FDA has progressed over the last decade to achieve a more systematic approach to incorporating patients' experiences and priorities into the clinical testing process. Efforts to identify what is most important to patients regarding burden of disease and treatment preferences have become important in designing protocols and research strategies most likely to address medical needs and risks.

Congress has signaled strong support for such initiatives: the latest Prescription Drug User Fee Act (PDUFA VI) authorizes additional strategies for utilizing the "patient's voice" in assessing the burden of disease and treatment most important to patients. And the 21st Century Cures Act calls on FDA to develop guidance on methods for collecting "relevant, objective, accurate, representative, and meaningful patient experience data" throughout drug development. In finalizing FDA's budget for 2019, the House Appropriations Committee specifies the importance of considering patient experience information in the review of new medical products and relevant product labeling to inform treatment decisions and "payer determinations."

FDA is responding with initiatives to better coordinate patient input activities for drugs, biologics, and medical devices. A new Patient Affairs Staff (PAS) in the Office of Medical Products and Tobacco (OMPT) is collaborating with the National Organization for Rare Disorders (NORD) to hold a series of listening sessions to further incorporate patient experience with rare diseases into regulatory decision-making. PAS also has launched the Patient Engagement Collaborative with the Clinical Trials Transformation Initiative (CTTI) to establish an outside group able to provide regular patient views to FDA. The CTTI collaborative is similar to the Consumers' Working Party of the European Medicines Agency (EMA). Separately, FDA and EMA formed a Patient Engagement Cluster in 2016 to discuss best practices and experiences in this area on a more formal, regular basis.

PDUFA and the Cures legislation both instruct FDA to issue multiple guidances on collecting and submitting patient experience data to FDA to enhance how the agency uses it to inform decision-making. The advisories will assist sponsors in assessing burden of disease and burden of treatment most important to patients, how best to identify measures in clinical trials that matter most to patients, and how to use such measures as endpoints significant for regulatory decision-making. These and other topics will be discussed at FDA public workshops in the coming months.

Seeking new strategies

The new PAS initiatives reflect a shift at FDA from expanding on the 24 PFDD meetings conducted since 2014 to strategies to incorporate more clearly the wide range of patients' perspectives gained from these meetings into credible evidence that can support product development and regulatory decision-making. The aim is to identify best practices for identifying meaningful patient data and new programs and policies to utilize this information.

Insight and advice for achieving this goal may arise from an initiative to advance the science of patient input to achieve more rigorous, credible evidence for use in medical product R&D. At a workshop in May, organized by the Forum on Drug Discovery, Development and Translation of the National Academies of Sciences, Engineering and Medicine (NASEM), experts from industry, disease organizations, academic research centers, and government agencies discussed optimal methods for collecting patient experience reports, barriers to this process, and how these initiatives relate to the drive to tap real-world evidence and other information sources useful to decision makers (see https://bit.ly/2HbMFOO).

Theresa Mullin, associate director for strategic initiatives in the Center for Drug Evaluation and Research (CDER) and head of the PFDD program, noted that many drug development programs do not ask patients early enough about setting eligibility criteria, avoiding barriers to trial participation, and what endpoints are most meaningful in dealing with a disease. Mullin outlined how FDA seeks to better understand those aspects of a disease that matter most to patients and whether such attitudes vary by age, culture, or severity of disease. A related question is which commonly measured endpoints are most relevant to different patient subgroups. FDA seeks ideas for dealing with clinical trials that exclude patients who want to participate and with study protocols that are intolerable or unworkable for some individuals. And the agency wants information on measures that may increase the likelihood of patient enrollment and retention in a study and what challenges patients may face in trying to adhere to a prescribed drug regimen.

Workshop participants discussed a range of strategies for improving the measurement and collection of patient experience data, including the use of registries to identify in advance those patients who meet enrollment criteria. The goal is to outline in a report where further research may advance methods for soliciting patient input in research processes that reflect the needs and preferences of affected populations.

— Jill Wechsler

FDA NOTES

The following committee meetings are scheduled for June and July:

- The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee ***June 20***
- Blood Products Advisory Committee Meeting Announcement ***June 22***
- Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee ***June 26***
- Blood Products Advisory Committee Meeting Announcement ***July 18-19***

EU REPORT

POLICY AND PRACTICE COME TOGETHER ON EU VACCINE THRUST

It's only a matter of a few weeks ago that the European Medicines Agency (EMA) released a revised guideline on the clinical evaluation of vaccines. This wasn't the result of EMA prescience that a new outbreak of Ebola fever in the Democratic Republic of Congo in mid-May would concentrate attention yet again on the world's lack of adequate vaccines. It was triggered by more scientific concerns. But a convergence of pressures—both policy-driven and practical—has imparted renewed urgency to the European Union's bid to up its game on effective immunization.

First, the draft of the updated guideline (https://bit.ly/2k6B1vk)—which everyone has an opportunity to comment on until the end of October. This "introduces additional safeguards for European Union citizens and ensures that the evaluation is in line with the most up-to-date scientific knowledge and technological developments," says EMA. And it includes specific considerations for clinical trials in special populations, such as pregnant women or the elderly.

The revised version of the guideline also focuses on strategies for priming and boosting, including heterologous prime-boost in which one type of vaccine is followed by a different one for the same pathogen. In an oblique reference to the Ebola-type scenario, it also covers "the need to develop vaccine for pathogens that may cause future epidemics and for which conducting clinical trials outside of outbreaks might be problematic."

It is a response to innovations that raise issues for clinical development programs, such as vaccines that include antigenic substances from multiple pathogens or from multiple subtypes of a single pathogen, or the conduct of efficacy trials or identification of immune correlates of protection. It also includes a discussion of factors to consider when planning and interpreting the results of comparative immunogenicity trials—such as the severity, mortality, or risk of permanent sequelae of the infectious disease to be prevented.

It looks at the robustness of the assays to determine the immune response when selecting non-inferiority margins and assessing the clinical impact of failing to meet pre-defined criteria. And in trials that compare candidate and licensed vaccines containing antigens from different numbers of subtypes of the same organism, it comments on interpretation of immune responses to non-shared subtypes.

But EMA's essentially scientific focus fits conveniently within the broader context of EU policy, which has itself been in rapid evolution recently. In April, the EU unveiled a new draft strategy for member states to cooperate on vaccination, in which the industrial and research aspects of vaccines feature prominently. EU health ministers are to examine the recommended approach later this year with a view to giving it formal status. And the EU will set up a new joint project on vaccination among EU member states this autumn.

Noting that EU citizens are at risk in the face of epidemics because "production capacities in the EU remain limited," the strategy urges efforts to be made "jointly with stakeholders and industry, improving EU manufacturing capacity and ensuring continuity of supply." Among the wider challenges related to R&D, the text recognizes the difficulties of developing new innovative vaccines, and highlights the "complex, costly, and risky" improvement of existing vaccines to improve the safety profile, or adapt to different ages, risk groups, or pathogens.

To move R&D forward requires "substantial financial investment and expertise," it says, recommending the creation of "innovative partnerships and platforms, high-level expertise, and stronger interlinks between disciplines and sectors." National governments should "increase support to vaccine research and innovation," and the efficiency of EU and national vaccine R&D funding should be raised, it argued. This should be promoted through new partnerships and reinforced research infrastructures, "particularly for clinical trials." And EMA should be more closely involved in early dialogue with developers, national policymakers and regulators "to support the authorization of innovative vaccines, including for emerging health threats."

It isn't just at EU level that the attention is focused on collaboration. The World Health Organization's (WHO) annual assembly was set to debate last month on how to address the global shortage of medicines and vaccines, against the background of a promise from the WHO secretariat to "work in support of greater consensus among member states on establishing effective policies on access to medicines, vaccines, and health products." This is in fulfilment of WHO's work toward achieving universal healthcare, in line with the targets of the United Nations' sustainable development goals that notably include "access to safe, effective, quality, and affordable essential medicines and vaccines for all."

But the challenges are not just scientific or technical or even logistic. There is plenty of evidence of difficulties posed by growing skepticism over the merits of vaccination. Outbreaks of measles—even resulting in deaths—have occurred recently in pockets across Europe where vaccine hesitancy among the local population has led to sharp drops in immunization. More than 14,000 people contracted measles in the EU in 2017—more than three times the level of 2016. Fifty-seven deaths due to measles have been reported since 2016.

The European health commissioner, Vytenis Andriukaitis, himself a physician, has been a passionate opponent of this trend. "It is unacceptable that children are still dying of measles in the European Union," he said recently. It was at his insistence that the new EU strategy on vaccination emphasizes the need to tackle vaccine hesitancy and to increase vaccination uptake.

Exploring the reasons for the trend, Andriukaitis remarked: "Across Europe, more and more people are avoiding vaccination. Why? Well, misinformation by vaccine deniers, the rapid spread of fake news, public distrust, and the fears of possible side effects all play a role." And misinformation is available in abundance, in the EU and elsewhere.

— Peter O'Donnell

CLINICAL TRIAL INSIGHTS

THE NEED AND OPPORTUNITY FOR A NEW PARADIGM IN CLINICAL TRIAL EXECUTION

Sobering statistics point to the eventual convergence of healthcare and clinical research operating environments

Ken Getz

Demand for new clinical trial models is intensifying given the high and rising cost and chronic inefficiencies associated with finding and engaging investigative sites and study volunteers.

A recent study conducted by the Tufts Center for the Study Development (Tufts CSDD) found that sponsors and contract research organizations (CROs) spend, on average, 31.4 weeks (nearly 8 months) from site identification to site activation (i.e., ready to begin enrollment)—15% longer than the average duration observed 10 years ago. Although the duration is 10 weeks shorter for repeat or familiar investigative sites, in any given multicenter study, 28% of investigative sites have no prior history and are new relationships for CROs and sponsors.

The proportion of novice investigators is expected to rise as new investigational treatments target rare disease and more stratified patient subpopulations. Protocol designs are already being impacted by this shift. Phase II and III protocols have seen an average 60% increase in the total number of inclusion and exclusion criteria per protocol during the past decade. Increasingly, eligible patients can best be found among select physicians—typically unfamiliar with industry-funded clinical trials—who specialize in small, narrowly defined patient communities.

The lengthy time commitment put into the overall investigative site initiation process does not guarantee successful patient enrollment. In past columns, I have touched on a number of discouraging findings indicating that patient recruitment and retention rates have steadily worsened. Across all therapeutic areas, for example, the planned patient enrollment duration in the typical Phase II and III clinical trial must be doubled to complete actual enrollment of the targeted number of patients. Even after doubling planned enrollment duration, 11% of initiated investigative sites in Phase II and III clinical trials will fail to enroll a single patient and nearly four-out-of-10 initiated-investigative sites will under-enroll. This latter group is the most expensive because these sites have been activated and now must be supplied with clinical trial provisions and monitored to ensure compliance and quality.

An ill-suited landscape

Unrealistic timelines and the heavy burden placed on principal investigators (PIs) and study staff to administer highly demanding protocols partially explain site performance experience. But our analysis of more than half-a-million form 1572 records in the FDA's Bioresearch Monitoring Information System (BMIS) reveals that sponsors and CROs continue to engage a global investigative site landscape that is predominantly inexperienced, minimally active with limited infrastructure, poor continuity, and lacking in adequate patient volume.

At the end of 2017, there were approximately 38,000 unique FDA-regulated PIs worldwide. Approximately two-thirds of all global investigators still participate in only one clinical trial annually and each year during the past decade approximately one-third of all unique FDA-regulated PIs are first-time filers, having never before participated in an industry-funded clinical trial.

Turnover rates are also very high, particularly among the majority of investigators conducting a small number of trials each year. In our recent analysis, about four-out of-10 unique FDA-regulated PIs worldwide who filed at least one form 1572 in 2011 have yet to file again. The high turnover is attributable to onerous regulatory requirements, heavy workload and time commitments, high study staff turnover, financial risk, and lack of sufficient financial incentives.

Fifty-five percent of all investigators are physicians in small, part-time, community-based settings unaffiliated with academic medical centers and health systems. These sites primarily deliver clinical care while dabbling in clinical research. These physicians have made progress in digitizing their patient medical records and in professionalizing their management and financial controls, but they treat a relatively small volume of patients. And most are ill-prepared to accommodate the more complex trials involving advanced biologics, new trial designs (e.g., adaptive clinical trials), and the use of new technologies like smart phones, mobile applications, and wearable devices.

Approximately 5% of the total—less than 2,000 FDA-regulated investigators—operate within larger, community-based dedicated site networks. This segment is relatively sophisticated, with IT and operating infrastructure better suited for managing a higher volume of, and more complex clinical trials, but with relatively modest patient volume. Dedicated sites and site networks derive nearly all of their income from clinical trial grants—not from clinical practice—and the majority of their patients are recruited through advertising and outreach. Although this segment has been better positioned to manage large and demanding Phase II and III clinical trials, it is becoming less viable as sponsors and CROs seek stratified and rare disease patients matching far more elaborate eligibility criteria.

About 40% of total investigators are based within academic and hospital settings. This segment has access to a relatively large community of well-trained health care professionals, very large patient populations, and relatively sophisticated patient health and medical data. But, historically, industry-funded clinical trials in these settings have been more bureaucratic and inefficient. Tufts CSDD research has shown that clinical trials conducted within academic settings typically have the lowest activation and completion rates and they are consistently the slowest at enrolling patients.

Patient engagement, data, and analytics

Since 2010, drug development sponsors have embraced patient engagement principles, chief among them to provide the opportunity for patients to participate flexibly, wherever and whenever they can most easily and conveniently do so. Home nursing networks, digital and mobile health solutions, telemedicine, and direct-to-patient clinical trials are among the many convenience models that are being implemented—several customized depending on individual patient preferences per study.

New applications and systems capable of storing and managing large volumes of structured and unstructured patient data are also becoming more commonplace in clinical

CLINICAL TRIAL INSIGHTS

trials as biopharmaceutical companies embrace the collection and interrogation of data to support more complex scientific decisions, more sophisticated management of the R&D process, and continuous learning about patient response to investigative and commercially-available treatments.

Data from numerous sources, including unstructured feedback from patient and professional communities, is being used to support drug development planning, protocol design, site and patient identification, patient response and adverse event patterns, and study conduct convenience and performance. Predictive analytics and forms of artificial intelligence (e.g., machine learning) are being piloted and implemented by biopharmaceutical companies and CROs to help accelerate data processing and provide more rapid insight for drug development scientists and operating managers. Electronic health and medical records—particularly those that integrate diverse data elements—are among the most important data sources.

Integrated health delivery systems for large covered populations are uniquely positioned to provide rich patient data supporting industry demands for analytical rigor and sophistication. Health systems also provide the highest relative patient volume to support the identification of very targeted and rare subpopulations. According to the federal Agency for Healthcare Research and Quality (AHRQ), health systems in the U.S. include 70% of all hospitals and 50% of all board-certified physicians. In addition, the vast majority of U.S.-based health systems are certified electronic health and medical record users and have the capability to electronically query patient health data. Surveys among patients show that they would prefer to participate in clinical trials that are better integrated into their routine healthcare. Given their typically low and diminishing operating margins, health systems also appear eager to compete for new revenue streams, including that from clinical trials sponsored by drug development companies.

Concluding thoughts

My colleagues and I are beginning to model the economic impact of the convergence of clinical research into larger clinical care settings and I hope to report our findings soon. Our evolving assumptions include faster start-up and enrollment given the smaller number of high-relative patient-volume settings identified by rich data and sophisticated analytics. Several factors may contribute to lower study conduct costs, including the use of clinical research professionals operating flexibly within existing clinical care infrastructure, and better leveraged and engaged primary and specialty care professionals. Assumptions around factors contributing to higher costs include rising protocol complexity variables (e.g., number of procedures, eligibility criteria); the growing number of data collection sources, including wearable devices, mobile health applications, and real-world evidence; and the increasing number of participation convenience initiatives (e.g., concierge services, home nursing networks and telemedicine) supporting study volunteer enrollment.

> This convergence is inviting disruptive new clinical trial models offering higher levels of flexibility, customization, and integration.

Healthcare and clinical research operating environments will eventually converge as the public, providers, and payers demand access to more effective and affordable medical treatment options, and as industry strives for better performance and more cost-efficient R&D and commercialization capabilities. This convergence is inviting disruptive new clinical trial models offering higher levels of flexibility, customization and integration. It is also creating opportunities for existing study conduct service providers to adapt their services, capabilities, and operations and to merge with collaborative partners.

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

REGULATORY

NEW 'RIGHT-TO-TRY' LAW CHALLENGES FDA OVERSIGHT

After months of debate, Congress enacted legislation last month that establishes a pathway for terminally ill individuals to gain access to investigational products. Even though FDA has a well-established and effective expanded access/compassionate use program that assists very ill patients in obtaining not-yet-approved therapies from sponsors, agency critics have long demanded stronger action to remove roadblocks to experimental treatment.

FDA Commissioner Scott Gottlieb and previous agency leaders have maintained that this legislation is not needed and may expose desperate individuals to harmful or ineffective treatment. They also have concerns that the latest bill undermines FDA authority to vet and approve important new medicines based on safety and efficacy. Under pressure from the Trump administration, Gottlieb recently softened his opposition, stating that FDA can implement the new policy without harming agency operations or safeguards.

— Jill Wechsler

Q&A

CLINICAL TRIAL EVOLUTION: A CRO's PERSPECTIVE

Devinder Poonian, CEO of Rockville, MD-based CRO DP Clinical, discusses changes in clinical trial practice over the years, and the company's experiences with complex spinal cord injury trials.

Q: Your CRO has been in business over 24 years. What specific changes have you seen in the industry?

POONIAN: A great deal has changed in the CRO/drug development industry over the last 24 years. Patient participation as a result of greater awareness through advocacy groups and social media have had a significant impact on how patient recruitment is handled. We are now able to identify potential trial participants so much easier than before, and with difficult-to-enroll patient populations, this is extremely important.

Technology changes have also had a significant impact on the industry. Whether you look at how data management was handled in the past (paper case report forms, or CRFs) and the move to electronic data capture or the use of other trials tools—clinical trial management systems (CTMS) and electronic master file (eTMF) systems, there is no doubt that we have come a long way in how we conduct clinical trials. Other industry changes include product licensing, mergers and acquisitions of both pharma and CROs, as well as the development of creative approaches to the financial challenges of many startup companies pursuing new therapies.

Q: What specific changes have there been to clinical trials?

POONIAN: Technology has had the biggest impact on clinical trials. When DP Clinical started, data was captured on paper CRFs, monitored onsite, collected, and brought or shipped back to the CRO for data entry into the study database. Today, everything is electronic—EDC systems, remote and onsite monitoring, and almost real-time access to data. All this provides sponsors with the information they need to make informed decisions regarding their studies quickly, ultimately minimizing risk and reducing cost.

Q: As a small CRO, how do you respond to the big CRO/big pharma, little CRO/little pharma discussion?

POONIAN: To some extent, I agree. We have found that small pharmaceutical companies and biotechs have needs that can't typically be met by large CROs. Small/mid-sized CROs have much more flexibility to meet sponsor requests and can adapt quickly to their ever-changing requirements.

Having said that, we work well with large pharma also. They appreciate our focus, experience, and reputation; and they know we can deliver. At DP Clinical, we have successfully managed studies for all types/sizes of companies. We develop true partnerships with our sponsors and offer the personal attention they often don't get with larger CROs.

We've found that the CRO's experience, knowledge of the therapeutic area, quality of work, and reputation are more important than the size of the CRO or pharma. Finding a partner that you trust, is knowledgeable in the type of study to be conducted, and has a reputation for delivering are key.

Q: How did you get involved with spinal cord injury trials?

POONIAN: I started my clinical career with Fidia Pharmaceuticals, which specialized in products for neurological disorders. There I initiated the first acute spinal cord Injury (SCI) study at 32 neurotrauma centers in North America. I then went on to start DP Clinical, which combines a strong neurology/CNS research heritage with over 24 years of experience in conducting acute and chronic SCI clinical trials. Since 1994, we have worked on almost all of the major acute and chronic SCI studies conducted, starting with the benchmark study of Sygen® (GM1)—considered the gold standard in SCI treatment—as well as studies using autologous cells, stem cells, and devices.

Q: How difficult are these trials to conduct? What is involved?

POONIAN: Because of the small potential market size, large pharmaceutical companies have not invested in SCI research; however, small pharmaceutical and biotech companies have displayed an increased interest in SCI clinical trials, and it's a good fit for them.

SCI studies are very difficult, because they have an added level of complexity—sites must wait for someone to experience a life-altering event. It's traumatic, literally, for the patient; and study sites must wait for an event to occur as opposed to actively seeking patients. With improvements in car safety (airbags and seatbelts), fewer people are injured in car accidents, thus reducing the number of SCI patients each year.

Devinder Poonian

Potential patients are often treated at a hospital and would have to be transferred to a study site. This typically cannot be done within the study timeline which often require therapies to be administered within a few hours or days of the SCI. Additionally, many acute SCI patients are seen at Level II trauma centers and are not transferred to Level I centers where studies are actively enrolling. As a result, enrollment takes longer than some clinical trials and must be managed carefully by the CRO.

Finding the right trauma centers, with experienced staff able to conduct the necessary assessments is critical. Because there is variability among study sites and assessors, additional training must be provided to ensure consistency. CRO oversight is very important to these studies to maintain assessment and data accuracy. We have worked with numerous centers to train and support them in patient enrollment.

Many companies interested in conducting SCI research are small and funding can be difficult, because SCI studies are costly. To meet enrollment requirements, especially for larger SCI clinical trials, it may take several years to recruit and enroll the needed number of SCI patients needed. So, long-term funding becomes an important element in SCI trials. To date, there have been no FDA approved treatments for SCI and only a few trials have shown patient improvement.

— Staff Report

LEARN MORE ABOUT

FUNCTIONAL SERVICE MODELS REIMAGINED

Integrating services and innovation for accelerated clinical development

On-demand webinar

Aired June 6, 2018

View now for free!

www.appliedclinicaltrialsonline.com/act_p/innovation

PRESENTERS:

Renee LaFaive
Vice President, Global FSP Business Development, IQVIA

Denitsa Simeonova
Head of Innovation, Global Functional Resourcing, IQVIA

MODERATOR:

Lisa Henderson
Editorial Director, *Applied Clinical Trials*

Moving between full-service and functional service outsourcing models isn't new for pharmaceutical and biotech companies – but why they choose which model is shifting. Clinical outsourcing choices have traditionally been based on needs to fill gaps and manage capacity. However, today's increasing regulatory hurdles and commercial competition are driving sponsors to evaluate outsourcing models on their ability to accelerate programs.

Attend this live webinar to learn how IQVIA's functional service provider (FSP) model is infusing advanced analytics, expertise and transformative technology to save sponsors time and money.

Key take-aways:

- Top 3 myths of FSP models debunked
- FSP case studies illustrating increased productivity and changing behavior
- What's next – the evolution of FSP

Presented by:

Applied Clinical Trials

Sponsored by:

IMS Health & Quintiles are now IQVIA™

CONTACT US
iqvia.com

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

ACT ONLINE

GO TO:
appliedclinicaltrialsonline.com
to read these exclusive stories and other featured content.

TOP 3 SOCIAL MEDIA

1. How Does GDPR Affect Clinical Trials?
   https://bit.ly/2EBUjRh
2. CRA Skills Lacking in Critical Areas
   https://bit.ly/2xQVFt0
3. Interventional vs. Non-interventional Study Classification
   https://bit.ly/2xGCuCe

eLEARNING:
This webcast will discuss why risk-based monitoring (RBM) is more than just source document verification and remote monitoring, and what companies need to fully implement RBM, including trained people, a robust process, and an integrated technology platform for quality management at every level.
https://bit.ly/2Jg5GWl

As *Applied Clinical Trials* continues its move to a more enhanced digital experience, be sure to visit our online digital edition of the magazine, with the same look and feel as the print! The Digital Edition Archive (link below) features a quick list of the contents for each issue.
http://bit.ly/2AB7F2p

Headlining our Surveys page (https://bit.ly/2kNTuxb) is SCORR Marketing and *Applied Clinical Trials*' recent effort to gain insight into the best strategies to attract and retain clinical research talent. Information provided includes which types of companies are sources of talent and the destinations of lost talent; incentives used to attract and retain talent; what tactics companies prioritize when hiring and recruiting new employees; and which positions are most difficult to replace.
https://bit.ly/2LkzzBd

NEWS NOTES

CRO: FEDERAL TAX SUPPORT KEEPS AUSTRALIA COMPETITIVE FOR CLINICAL TRIALS

Sydney, Australia-based contract research organization (CRO) Novotech commended the recent Turnbull Government's Federal Budget decision to exclude clinical trials activity from a $4 million cap on cash refunds, or any lifetime cap on refunds.

Novotech CEO John Moller, MD, said the move reaffirms Australian's lead position in attracting foreign investment for drug development and sends a message to the international biopharma community that Australia is the place to conduct research.

"The clinical trial sector not only delivers around $1 billion to the Australian economy annually, it also supports the Australian biopharma industry growth and expertise for the development of new life-changing therapies for both the Australian and world markets," said Moller.

Novotech, established in 1996, has offices in 11 countries throughout the Asia-Pacific region. "More than $650 million in clinical trial investment each year comes from overseas biopharma companies wanting fast yet high-quality research. According to our clients, the R&D Tax Incentive is a significant factor in their decision to invest in Australian research," added Moller.

Animal studies and human safety

A big data analysis conducted by Elsevier has evaluated the ability of animal studies to predict human safety. The statistical study examined the consistency between preclinical animal testing and observations made in human clinical trials. The study analyzed 1,637,449 adverse events reported for both humans and the five most commonly used animals in FDA and EMA regulatory documents, for 3,290 approved drugs and formulations. The results revealed that some animal tests are far more predictive of human response than others, depending on the species and symptom being reported. This finding, which also has considerable implications for improving patient safety, can help pharmaceutical companies decide which tests are appropriate and which might be ruled out to reduce unnecessary testing on animals.

One of the main conclusions of the study, published in the *Journal of Regulatory Toxicology and Pharmacology*, is that when it comes to cardiac events such as arrhythmia there is a high degree of concordance between animal and human responses. However, at the other end of the spectrum, some events are identified have never been reported in a human, and some events observed in humans have never been reported in an animal study.

LMC Manna Research adds Omnispec

LMC Manna Research—the largest network of fully-owned and integrated clinical research sites in Canada providing Phase I-IV clinical trial services—has acquired Montreal-based research center Omnispec Clinical Research. Having contributed to the development of more than 60 drugs, Omnispec adds greater capacity, data, and talent to the LMC Manna Research network.

Lilly expands cancer pipeline

Eli Lilly and Co. has agreed to acquire AurKa Pharma Inc., a company established by TVM Capital Life Science to develop an early-phase oncology compound, an Aurora kinase A inhibitor that was originally discovered at Lilly. The drug is a potential first-in-class asset in Phase I trials in multiple types of solid tumors. Aurora kinases are believed to play a crucial role in cellular division by controlling chromosomal segregation. Aurora A, B, and C are key mitotic regulators required for genome stability and are frequently overexpressed in cancerous tumors.

Elligo acquires ePatientFinder platform

Elligo Health Research, which improves clinical trial access by engaging the 97% of physicians currently not offering clinical research to their patients, has acquired ePatientFinder's Clinical Trial Exchange technology platform and referring practice network, which is the largest of its kind. The acquisition will enhance Elligo's trial matching process by incorporating ePatientFinder's technology platform. Using this platform, Elligo will streamline patient identification and feasibility through automation using electronic health record (EHR) data within Elligo's network of providers.

— Wire Reports

REGULATORY

TURNING EU HTA REFORM INTO LEVEL FOR CONTROLLING DRUG DEVELOPERS

At first glance, there would appear to be nothing remarkable in the following statement about health technology assessment (HTA): "HTA should be instrumental in promoting innovation which offers the best outcomes for patients and society as a whole."

What makes it remarkable is its prominent place in the latest contribution to Europe's increasingly heated debate on reshaping HTA for the future. It comes in the first paragraphs of a document from the European Parliament, drafted by the member of parliament who has been appointed to oversee the discussions of the proposed new scheme.

Soledad Cabezón, the MEP in question, is no great admirer of the pharmaceutical industry, and the report she has drafted displays her skepticism about the motivation of the European Union's bid to improve HTA. The European Commission's proposed regulation to ensure greater EU-level coordination is, in her view, focused too much on industry, enterprise, and markets—to the detriment of wider patient and public interests.

That is why she wants to modify the wording of the proposed regulation, which says: "The development of health technologies is a key driver of economic growth and innovation in the Union." For Cabezón, the emphasis should be on people, not production.

The rest of her draft report reinforces this approach. At present, she says, "the main barriers to access to medicines and innovative technologies in Europe are the high price of medicines, in many cases without these being of added therapeutic value, and the lack of new treatments for certain diseases." And that, she suggests, is the consequence of insufficient control of what drug developers are doing.

She remarks that in the European pharma market: "A high percentage of marketing authorizations are not accompanied by a comparative effectiveness study." It is, of course, true. But it is, in effect, a truism. Because European legislation on the grant of marketing authorizations makes no provision whatever for comparative effectiveness studies.

The three criteria for approval remain uniquely quality, safety, and efficacy—just as they have been since the first EU legislation on the subject in the 1960s. Comparative effectiveness may well enter into the reflections of national authorities when they make their own national decisions on price or reimbursement status of a medicine, but the marketing authorization—which is covered by EU rules—does not require this.

Cabezón asserts that "a very high percentage of new medicinal products brought on to the European market offer no advantage over existing products." She is also critical of current clinical trials arrangements. "Of the clinical trials approved in the EU, only 30% involve more than 1,000 patients and a monitoring period longer than a year," she says.

Worse, "more and more medicinal products are securing early authorization, and those products are six times more likely to be withdrawn from the market and four times more likely to trigger significant alerts, and three times as many are withdrawn from the market," she claims.

So, Cabezón wants to see the EU HTA discussion veer away from the Commission's aims of streamlining and reducing duplication and unnecessary divergence, and instead toughen up controls on clinical trials and drug development.

She is calling for "the tightening of the rules on clinical evidence, including a coordinated procedure for the authorization of multi-center clinical research; the tightening of post-market monitoring requirements for developers of technology; and the improvement of coordination mechanisms in the fields of surveillance and market monitoring."

— Peter O'Donnell

DEALMAKING

TAKEDA AGREES TO $62 BILLION TAKEOVER OF SHIRE

Takeda Pharmaceutical Company Limited and Shire plc reached an agreement in May on the terms of a recommended offer pursuant to which Takeda will acquire the entire issued and to be issued ordinary share capital of Shire. Under the terms of the acquisition, each Shire shareholder will be entitled to receive $30.33 in cash for each Shire share and either 0.839 new Takeda shares or 1.678 Takeda ADSs. The transaction has been approved by both companies' boards of directors, and is expected to close in the first half of 2019. Upon the closing, Takeda shareholders will own approximately 50% of the combined group.

With leading market positions in prioritized therapeutic areas, an attractive geographic footprint, greater scale and efficiencies, and an even more productive R&D engine, the combined group will be better positioned to deliver innovative medicines and transformative care. The deal with bring together Takeda and Shire's complementary positions in gastroenterology and neuroscience, and will also provide the combined group with leading positions in rare diseases and plasma-derived therapies to complement strength in oncology and focused efforts in vaccines.

Takeda will continue to focus on the acceleration of its oncology business, following its recent acquisition of ARIAD Pharmaceuticals. In addition, Takeda's vaccine business will continue to address the world's most pressing public health needs.

Shire has expertise in rare diseases, a modality-diverse mid- and late-stage pipeline, enriched with large-molecule programs, as well as technologies in gene therapy and recombinant proteins. The combined group will build on existing partnerships, including Takeda's more than 180 active partnerships with academia, biotechnology companies, and startups.

— Wire Report

CLINICAL TECHNOLOGY

NEW WEAPONS AND NEW WARNINGS OVER HEALTH RESEARCH

Artificial intelligence (AI) is a "new weapon" in healthcare research, according to UK Prime Minister Theresa May, speaking in the north of England in late May. Determined to talk up the UK's capacities in life sciences as she negotiates her country's departure from the European Union, she urged the national health service and research-based firms to make fuller use of AI to "transform" diagnosis of life-threatening diseases.

"The development of smart technologies to analyze great quantities of data quickly and with a higher degree of accuracy than is possible by human beings opens up a whole new field of medical research," she said, highlighting the role of computer algorithms in inferring conclusions from information gleaned through patients' medical records, genetic data, and lifestyle habits.

Her officials have been throwing around forecasts that AI could help prevent tens of thousands of cancer deaths every year, and boost the battle to overcome heart disease, diabetes, and dementia, and May's speech triggered a chorus of support from health organizations and research charities. Cancer Research UK, which claims that halving the number of lung, bowel, prostate, and ovarian cancers diagnosed at an advanced stage could prevent thousands of deaths a year, described the government's plans as "pioneering".

But a report from the UK's Nuffield Council on Bioethics, issued the same week, raised what it described as "important questions" about the use of AI in healthcare. While AI has the potential to make healthcare more efficient and patient-friendly by speeding up and reducing errors in diagnosis and helping avoid human bias and error, the report says, it focuses attention on crucial issues of liability, dignity, and security. Hugh Whittall, Director of the Nuffield Council on Bioethics, says "the challenge will be to ensure that innovation in AI is developed and used in a ways that are transparent, that address societal needs, and that are consistent with public values."

The report offers plenty of initiatives where AI holds out new hope. It cites the Institute of Cancer Research's canSAR database that combines genetic and clinical data from patients with information from scientific research, and uses AI to make predictions about new targets for cancer drugs. It notes the AI "robot scientist" called Eve that is designed to make drug discovery faster and more economical. It recognizes that AI systems used in healthcare could also be valuable for medical research by helping to match suitable patients to clinical studies. And it notes examples of AI being used to predict adverse drug reactions—which are estimated to cause up to 6.5% of hospital admissions in the UK.

Ultimately the greatest challenge, the report suggests, may lie in the intrinsic nature of AI itself, its inability to possess human characteristics such as compassion.

However, underlying concerns still need to be addressed, insists the report. Clinical practice often involves complex judgments and abilities—and the debate around whether some human knowledge is tacit and cannot be taught, the report adds. It evokes a 2015 clinical trial in which an AI app was used to predict which patients were likely to develop complications following pneumonia, and, therefore, should be hospitalized. "This app erroneously instructed doctors to send home patients with asthma due to its inability to take contextual information into account," it states. And the report emphasizes the need that patients and healthcare professionals have for trust—noting that clinical trials of IBM's Watson Oncology were "reportedly halted in some clinics as doctors outside the US did not have confidence in its recommendations, and felt that the model reflected an American-specific approach to cancer treatment."

The report also points to more technical challenges, including the limitation of its use by the quality of available health data. Medical records are not consistently digitized, and current healthcare IT systems lack interoperability and standardization, digital record keeping, and data labelling.

But ultimately the greatest challenge, the report suggests, may lie in the intrinsic nature of AI itself, its inability to possess human characteristics such as compassion.

As a telling nuance on May's optimistic encouragement to industry, the Nuffield report points out that AI has applications in fields that are subject to regulation, such as data protection, research, and healthcare, and its development is so "fast-moving and entrepreneurial" that it "might challenge these established frameworks."

For Nuffield, the key question is not whether AI should be regulated, but only whether it should be regulated as a distinct area, or whether different areas of regulation should be reviewed with the possible impact of AI in mind.

— Peter O'Donnell

CLINICAL TECHNOLOGY

CLINICAL TRIAL MHEALTH UPDATE: AN EU PERSPECTIVE

The biopharmaceutical industry continues to explore how mHealth can change clinical trials, as the discussion continued at the recent Hanson Wade's mHealth for Clinical Trials EU Summit in London. Topics included challenges and expectations in digital health, hindrances impacting digital health adoption in clinical trials, and further defining patient centricity and decentralized trials.

Challenges, needs of digital health

While digital health is widely adopted in consumer markets, clinical researchers have different expectations with the use of digital devices in clinical trial settings. Daragh Ryan, clinical trials technology consultant at Actelion Pharmaceuticals, suggested there are gaps in current digital health devices for clinical trial implementation. Ryan indicated that researchers want connected devices that integrate seamlessly, have multiple remote sensors to capture objective data and clinical endpoints, and are validated and are medical grade to support regulatory submissions. However, Ryan elaborated that researchers experience something different; digital health devices exhibit limited connectivity options and provide no feedback into device and patient status, they have low bandwidth, demand higher frequency raw data and high power consumption which requires more patient support, higher patient burden, manual data uploads, and expensive data contracts with vendors. Moreover digital health devices from numerous vendors require integration and data synchronization, which adds to complexity, cost, and security concerns.

Ryan predicts that future technologies will have better connectivity (i.e., Bluetooth 5 and 5 G network connectivity), enhanced sensors and expanded sensor measurement types (i.e., activity, gait speed, respiratory rate, e.g., SB 02, heart rate), and longer battery/charging solutions.

Why aren't clinical trials digital yet?

Clinical trials are notoriously known to be a laggard when it comes to innovation due to the strict regulatory environment in which they operate and ensuring patient safety. In addition, there isn't much regulatory guidance on implementing digital health in clinical trials, and there are few validated digital health measures. According to Alistair Stuart, director of clinical projects and digital platforms at GlaxoSmithKline, digital health pilots are occurring in healthcare settings, however, they are experimental and episodic. While digital health in healthcare is paving the way for clinical trials, sponsors and CROs are not fully implementing digital health because the regulatory framework is still evolving, and data is siloed in a variety of databases, making data access and aggregation a challenge.

> While digital health is widely adopted in consumer markets, clinical researchers have different expectations.

Additionally, Stuart explains that vendor feasibility processes at sponsors are not aligned with novel technologies; for example, current due diligence is often conducted on PowerPoint presentations or paper, forcing study teams to take big risks with unproven technology pilots, while attempting to deliver on their study's objectives and endpoints. The process can be improved if it evaluates vendor business activities with critical success factors in clinical trials and enables teams to conduct head-to-head comparisons with other vendors.

What will it take to drive change?

According to Kai Langel, director of clinical innovation at Janssen, several factors will drive change. From the patient's perspective, driving forces include the centralization of many study procedures around the patient. For example, patients will have access to online doctors/nurses, home visits, community clinics, and general practitioners, and apps and wearable technology will empower data collection. Additionally, continuous measurement of patient satisfaction via surveys throughout the trial can enhance the clinical trial experience and patient engagement, as sites can intervene if patient satisfaction levels drop beneath a key performance indicator. Langel believes that clinical trial data quality, time, and costs, reducing site burden, and enhancing oversight will drive digital innovation from sponsors.

Defining decentralized trials

There have been several explanations for patient centricity and decentralized trials, as some have suggested hybrid models. Bryan McDowell, global program lead, digital development, at Novartis, helped clarify the definition of decentralized clinical trials by conferring that they are executed with patients spending some or most of their time outside of sites when conducting study visit procedures. To achieve decentralized trials, study teams need to develop protocols more efficiently through protocol feasibility networks, execute consenting through electronic informed consent forms (eICF), leverage eSource to electronically capture study data, use connected sensors and novel endpoints, and deploy electronic patient-reported outcomes (PROs) and patient engagement tools to enhance adherence and the clinical trial experience.

— Moe Alsumidaie is Chief Data Scientist at Annex Clinical, and Editorial Advisory Board member for and regular contributor to Applied Clinical Trials

Clinical Design: A Deep Dive

Uncovering the most active models—many with application in rare disease

Lisa Henderson

RARE DISEASE

In this recent peer-reviewed article, http://bit.ly/2kLUu4U, the authors explored master protocols and their increasing use in oncology. "The term master protocol is well accepted to represent an ongoing trial intended for the addition or removal of drugs, arms, and study hypotheses. Master protocols may or may not be adaptive, umbrella, or basket studies. They may be a collection of sub-studies or a complex statistical design or platform for rapid learning and decision-making. Whether umbrella, basket, or platform, a master protocol seeks to update the randomized clinical trial model for the genomic age," the authors state.

While this article specifically focuses on oncology, asking the question, "what will it take to make the master protocol a standard in oncology research?" master protocols and other innovative or adaptive designs are beneficial for many rare diseases.

With our survey partner, SCORR Marketing, *Applied Clinical Trials* asked respondents about their use and knowledge of clinical trial design, not specific to oncology or rare diseases. (The survey is available here to download: http://bit.ly/2sH7YCJ). Suffice to say, many respondents who indicated they used master protocols also conducted oncology and/or rare disease research. While master protocols may not be adaptive, adaptive trials, as well as basket trials, ranked first overall in implementation of trial designs.

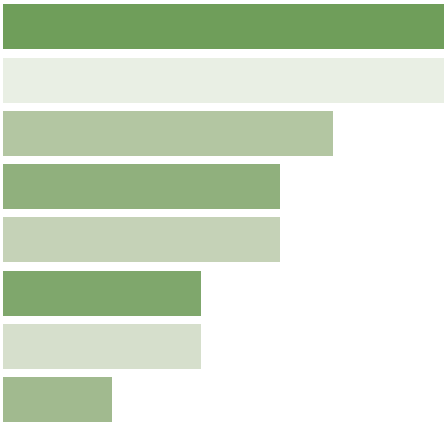
Adaptive trial design allows for modifications to the clinical development program based on how patients are responding, without undermining the trial's validity and integrity.

The primary goal is for a more flexible, efficient, and faster study. Adaptive clinical trials have come into their own since the FDA issued guidance around them in 2006.

Basket trials, on the other hand, have multiple arms (baskets) and can include a single drug evaluated in multiple malignancies or tumor site with the same target; a single drug evaluated as in the previous, but some may have different molecular targets; or multiple baskets representing multiple targeted agents that are evaluated in the same malignancies or tumors.

The basket trial design has limitations, primarily around the complexity of addressing multiple questions in a single protocol.

TYPES OF TRIALS IMPLEMENTED



Adaptive Trials	44.5%
Basket Trials	44.5%
Master Protocols	33.3%
Enrichment	28%
Hybrid	28%
Umbrella	20%
We don't implement these trial designs	20%
Other designs	11%

Source: *Applied Clinical Trials*/SCORR Marketing survey, May 2018.

Note: Respondents could choose more than one answer to this question. Responses to "other" included n of 1 trials and Bayesian design.

Regulatory authorities

With the increased use and acceptance of innovative and adaptive trial designs, both the FDA and the European Medicines Agency (EMA) offer scientific advice meetings for sponsors. In our survey, all respondents who said they conducted master protocols also said they solicit regulatory authority advice prior to designing their trials. A full 70% for all trial designs said that they do solicit that advanced scientific advice.

Recently, FDA Commissioner Scott Gottlieb highlighted past and future changes at the agency's Center for Drug Evaluation and Research (CDER) (http://bit.ly/2J7MoCl). Specifically, he noted "...the FDA has introduced many fundamental advances in how it evaluates drugs for safety and effectiveness, as well as the manner in which clinical trials are guided. These include adaptive approaches to clinical development such as the introduction of seamless trial designs or master protocols or tissue agnostic product approvals."

Gottlieb continued regarding the specific changes to organizational structures and processes at the FDA, which are intended to "allow our review staff to have more time for reviewing and providing feedback to sponsors on clinical protocols. One goal is to engage sponsors earlier in the development process to ensure that trial designs are efficient and structured in the most effective way to identify risks and measure benefit. Equally important, there will also be more ability to engage external stakeholders, such as disease specialists, academic researchers, and regulatory partners at other agencies. And with patient-focused drug development becoming a reality, ongoing relationships and interactions with patient groups are becoming an important part of our regulatory practices."

The EMA also offers scientific advice, and for 487 clinical trials hosted between 2009 and 2015, 244 requests for scientific advice were received by July 2017.

In this webcast, http://bit.ly/2kNq966, SGS Life Sciences offers expert insight into scientific advice with regulators, for EMA, FDA, and the individual, national European Union authorities. While experts explained sponsors can ask for advice at anytime during the drug's development, different points will offer different scenarios. For example, a European biotech with a compound in Phase IIa for women's health had meetings with both FDA and EMA. The discussion centered on:

- Set-up of the further clinical program
- Assessments to be done in the Phase IIb study
- Further non-clinical testing, in particular carcinogenicity testing
- Development plan for specific sub-indication

The company left with a clear outcome for its Phase IIb study, as well as improving assessments to its Phase III study. Other discussion points that SGS advised early in development included study design, development program, CMC aspects, and pediatric development.

Study innovation

In addition to designs, we asked respondents about the trial innovations they are using or plan to use. The majority responded that they are using EHR data (63%), followed by siteless studies (31%), blockchain (17%), and semantic technology (14%).

At a recent conference, CEO of Sarah Cannon Research Institute, Dee Anna Smith, presented the components of its cancer data warehouse. Those included its "systems" such as Epic; bone marrow transplant solution; radiation oncology EHR; cancer registry; and cancer navigation system. Data from the molecular profiling labs and affiliated medical oncologists EMR were also included in the warehouse.

Sarah Cannon is part of the larger HCA health network, and using the data from the warehouse, Smith said the company was able to identify 17,383 patients with breast, colon, gastrointestinal, and lung cancer. Of those, 6,092 were newly diagnosed and were navigated through Cannon and retained as patients. Keeping patients within the HCA system helps them access to the clinical trials through Sarah Cannon, and not be referred out of the system for care.

All respondents who said they conducted master protocols also said they solicit regulatory authority advice prior to designing their trials.

Siteless studies, also called remote, decentralized or virtual trials, have been an increasing choice for clinical operations in looking for more patient-centric choices. Siteless trials use digital technology to allow some or all aspects of a clinical trial to be carried out at a participant's home or local physician's office, rather than at a central trial site such as a large hospital.

In early March, Novartis announced that its alliance with Science 37 would initiate up to 10 new clinical trials over the next three years. The studies will blend virtual and traditional models, with increasing degrees of decentralization toward a mostly siteless model. Novartis was an early investor in Science 37, a decentralized clinical trial technology and design provider that uses its proprietary Network Oriented Research Assistant (NORA®) technology), which enables patients to participate in studies using mobile devices and telemedicine services. To date, Novartis and Science 37 have initiated virtual trials for cluster headache, acne, and nonalcoholic steatohepatitis (NASH). The decentralized trials are expected to begin later this year in the US in the areas of dermatology, neuroscience, and oncology. In May, UCB also announced the use of NORA in its trials.

Our survey did tackle a number of other questions, including gains or benefits expected by using innovation or different trial designs. All received about a 70% score in the following: better quality data; better recruitment/retention; cost savings; faster executive and regulatory compliance.

Respondents also noted that adaptive trials and studies that use EHR data provide the highest return on investment.

A 'Rare' View on Realizing Treatments for Unmet Need

Joe Wiley, CEO of UK-based Amryt Pharma, is steering a road-less-traveled path from the small-pharma playbook—building a sustainable, commercial infrastructure first, with the hopes of accelerating late-stage rare disease drugs to the patients who need them in Europe and beyond

Joe Wiley, CEO of London-based Amryt Pharma. (Photo courtesy of Amryt Pharma)

Julian Upton

UK-based Amryt Pharma launched in 2015 as a commercial-stage enterprise focused on developing and delivering innovative new treatments for rare and orphan diseases. The company pursued a different path in taking a commercialization focus from the start, with the aim of identifying late-stage assets and bringing them to market in Europe, the Middle East, and North Africa. Amryt's in-licensing of and subsequent success with homozygous familial hypercholesterolemia (HoFH) treatment Lojuxta was a milestone in its development, quickly facilitating the company's transformation from a development-stage to a commercial business. HoFH is a very rare and life-threatening genetic disorder characterized by extremely high LDL cholesterol levels.

Applied Clinical Trials spoke to Amryt CEO, Dr. Joe Wiley, to chronicle the rapid rise of this young company, and to discuss how he aims to maintain this momentum in the changing pharma landscapes of Europe and the US.

Could you outline the Amryt story so far?

WILEY: I set up the business with my partner, now CFO, Rory Nealon in August 2015 and it's been quite a rollercoaster since then. I'm a medic by training, and before setting up Amryt I worked for Sofinnova Ventures, a US venture capital group, one of the largest investors in biotech in the world. I opened and led the European office for Sofinnova and that role gave me a lot of visibility on all the late-stage drug development companies across Europe.

I noticed some very interesting dynamics, one being that the quality of the assets being developed and discovered here in Europe were every bit as good and often better than the assets being developed in the US. However, predominantly, the companies that are formed and the number of products going through clinical trials to the market is in the US because of access to capital. When you dig into the numbers, there's actually 10 times less capital to support European companies developing these assets. We felt that created an opportunity.

We set out to bring a really great team together, located in and initially focused in Europe. We wanted to be a commercializa-

tion business from the start. The way we would get over the access-to-capital issue would be to access the public markets here in Europe faster than you might ordinarily do in the US. In terms of the strategy of that business, the one thing that I've learned in 20 years in this industry, both on the investment side and on the operational side, is that if you focus on areas of really high unmet medical need, that's the best place to be for patients, because you're developing drugs that patients really need.

Of the 7,000-plus rare diseases known in the world, there's only approximately 600 or so drugs available to treat them. Rare disease patients are in desperate need of therapy, as often there's no therapy available for them at all. This also applies for physicians for the same reasons, and for investors and shareholders because there is higher likelihood of success when there are no other drugs. That's particularly true in rare and orphan diseases. So we decided to focus on that.

What were the challenges and advantages of building a company that avoids early stage R&D? Did setting up a different type of pharma company lead to any obstacles?

WILEY: We made that strategic choice quite deliberately. We decided early on that we didn't want to be a discovery company. As you know, in the pharmaceutical industry, the average cost of developing drugs keeps increasing; it's now certainly north of a billion dollars. That doesn't mean it costs a billion to develop a product, but it factors in the very high failure rate. Second is the length of time that it takes to develop a drug, an average 14 years to get a drug from discovery to the market. We didn't want to take that path, because that's incredibly long, incredibly capitally intensive, and very hard for shareholders to see a return on their investment in a timeframe that would be appropriate for particularly accessing public markets.

We felt that because there was an opportunity to build a great team with a commercial focus, that would be our core and our niche, and we would be able to identify those assets in Europe and successfully commercialize them and bring them to patients in need. And we've been very successful in doing that from a standing start. In December 2016, we in-licensed Lojuxta, which we leveraged to then build out our commercial infrastructure across Europe and across the Middle East, which constitute the main part of our licensed territories.

Under our stewardship, we've grown the product very significantly. Most recently, we in licensed a gene therapy platform for the treatment of a rare disease called epidermolysis bullosa (EB), which gives us a high-tech pipeline as a platform and potential to create a number of further products. What we're looking to do now is to add further commercial-stage assets down the channel that we've created. We're truly a billable company at this point because we've built our commercial infrastructure; we've got feet on the ground across Europe, across the Middle East, and we're headquartered in the UK.

Our topical wound care product for EB, AP101, is in a Phase III trial that is being conducted in Europe, South America, Asia, and Australia. It is the largest global Phase III trial ever conducted in EB (a group of inherited connective tissue diseases that cause blisters in the skin and mucosal membranes). We anticipate filing an [investigational new drug application] with the FDA to enable the opening of US trial sites in Q3 2018.

> When you dig into the numbers, there's actually 10 times less capital to support European companies developing these assets. We felt that created an opportunity.

AP101 is a topical product that we gained from acquiring a German business and works by accelerating wound healing. EB is a dreadful disease. It's a defect in the gene that codes for the protein that holds your skin together. Children born with this disease are called Butterfly Children because their skin is likened to the fragility of a butterfly's wings. Even pulling on socks can cause the skin to break. And there's nothing to treat the disease; no drug has ever been approved.

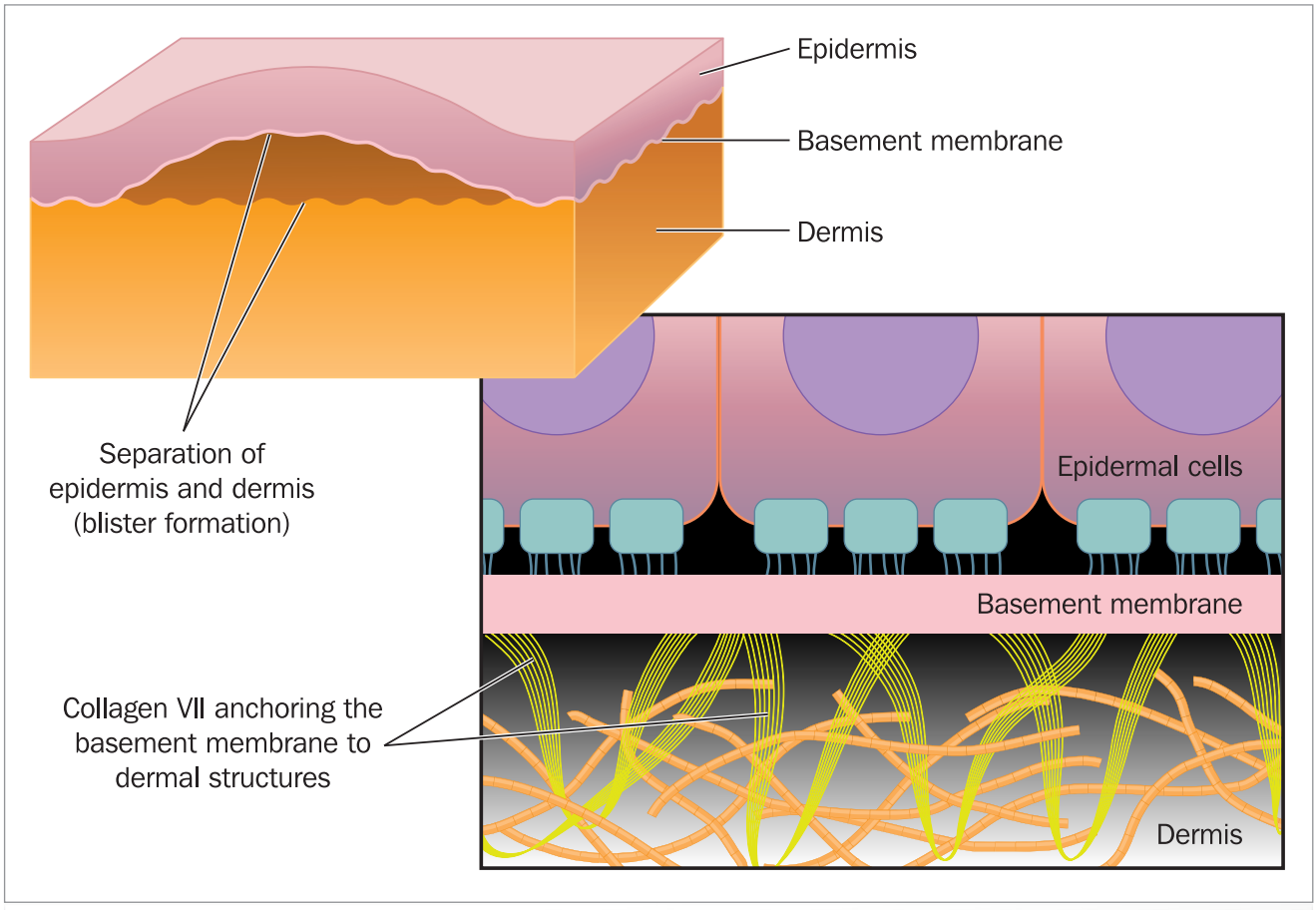
Our product has shown promise in a proof-of-concept study in EB and has successfully completed three positive Phase III studies in broader indications, which in fact led to the approval of that product by the EMA in partial thickness wounds in adults. This is a slightly unusual situation in that the product is actually approved in Europe, but has a very broad label. Our vision and our *raison d'etre* is, however, to focus on the rare disease with the really high unmet need, such as treating patients with the more severe forms of EB, both children and adults. While it's a very large market opportunity for us, it is also feasible to reach as a small company.

At a Glance

» Before joining Amryt Pharma, Joe Wiley opened and led Sofinnova Ventures' European office, was medical director at Astellas Pharma, and held investment roles at Spirit Capital, Inventages Venture Capital, and Aberdeen Asset Management (UK).

» While with Astellas, Wiley liaised with the marketing team and was involved in the launch of a number of specialty pharmaceutical products.

» Wiley trained in general medicine at Trinity College Dublin, specializing in neurology. He is a Member of the Royal College of Physicians of Ireland and has an MBA from INSEAD.



A drawing of blister formation in skin diseases such as epidermolysis bullosa, where the epidermis separates from the basement membrane and dermis.

If we could touch on the in-licensing of Lojuxta, how important was that for Amryt's early development?

WILEY: As I mentioned, from the outset, we wanted to be a commercial business and Lojuxta has enabled that. This is a product that we were able to in-license, which had been launched in Europe in 2013. We saw an opportunity to grow that product, and build out our commercial infrastructure on the strength of that deal. It transformed us from a development stage business to a commercial business overnight. And, importantly, because of how that deal was structured, it allowed us to build out that commercial infrastructure through investing on the back of revenues generated from this product. The revenues of the product actually paid for the roll-out of our commercial infrastructure.

One of the advantages of focusing on rare and orphan diseases with high unmet need is that the small number of patients affected by the disease means there's usually small numbers of physicians in specialist centers treating those patients; therefore, a commensurately small commercial footprint is sufficient to commercialize the products in this area. That works for us as a small company. Clearly, we can't launch a primary-care drug where we would have to visit every general practitioner in every country. But in rare and orphan diseases, we can. We've signed five new distribution agreements in the last few months, with key partners in the territories for which we have the license.

Can you talk about how you assembled the first management team and the importance of all their experience in getting the company off the ground?

WILEY: I was very fortunate in that, from the very outset, I was working with a tremendous partner and CFO, Rory Nealon. Rory and I have very complementary skill sets. We're both very transactional. In his previous career, I believe Rory did 12 acquisitions in 14 years at Trinity Biotech, which was another business that grew through acquisition. And for many years, I worked in the venture capital industry, investing in many companies in this area. We were also blessed to have Harry Stratford on board from the early stages, advising us on how he built his company, Shire, and later ProStrakan, from the ground up. We brought in Mark Sumeray, who has vast experience, fairly soon after we had done our first two acquisitions. David Allmond joined us as chief commercial officer, from Aegerion, and he has been very successful at building out our commercial team.

Somebody said to me that, combined, we have 170 years of experience in the industry. Across the leadership team, we have a great breadth and depth of experience across multiple therapeutic areas and geographies across the globe.

> One of the advantages of focusing on rare and orphan diseases with high unmet need is that the small number of patients affected by the disease means there's usually small numbers of physicians in specialist centers treating those patients.

What is your vision for the next three to five years? Are you concerned that you can keep a track on all that expertise as you grow?

WILEY: A lot of people say that we've built a company that looks and feels and operates like a much larger company. That's a reflection of that senior team and it flows through the rest of the business. We have a manufacturing facility, we've put the quality systems in place, we have the necessary infrastructure. We are able to leverage that now into a growth trajectory. Our core strategy is to launch our product that's in Phase III ourselves in our core markets. We see our core markets as Europe and the US, so we'll build out our commercial infrastructure in the US on the success of our EB product and we'll launch that in the US.

In the meantime, we would like to bring more products into our existing infrastructure, and leverage the infrastructure we've put in place, because then we will take advantage of economies of scale. Our strategy is to build and create a sustainable, European-based business for our shareholders and the stakeholders that will grow into the future.

Talking of Europe brings us to the obligatory question about Brexit. What are your views on that, with Europe being a major part of your plans and your current operation?

WILEY: So far, I would say that the impact has been minimal. Obviously, there's a concern, for sure. We're a UK plc operating in a global environment with a pan-European commercial business. So how that separation will work out is of concern.

There are two points, specifically. One is access to talent. We really hope that there will still be ongoing access to the top talent, because right now we are able to access that across Europe. The second area of concern for us is the unknown, specifically, what will happen regarding the regulatory environment? How that will look post-Brexit. Currently, EMA is in the process of transitioning from a London base to an Amsterdam base.

In rare and orphan diseases, products are approved through the centralized process, which means that you have a seamless regulatory process to get products approved across the whole European Union. What Brexit will mean for that remains to be seen. We hope and anticipate that the UK will remain in harmony with this process in the future.

— Julian Upton is the European and Online Editor for Applied Clinical Trials' sister publication, Pharmaceutical Executive

Gene Therapy in Rare Disease Research

A look at home and dosing site considerations

Mariah Baltezegar

With the rise in gene therapies entering clinical trials, it is important to address the operational challenges associated with these types of trials. Some gene therapy trials necessitate centralized dosing like those that require patient samples to derive the investigational medicinal product (IMP), which call for a limited number of dosing centers.

In this case, the patient may initially be seen at one center for evaluation, dosing, and initial follow-up, and subsequently seen at another center for their longer-term follow-up activities—in some cases, these may be in different countries. Because the prevalence of patients in the rare disease space are just that—rare—special considerations must be made to ensure patient access to the clinical trials.

This creates significant logistical challenges not only from a patient and family standpoint but from a regulatory and data collection standpoint as well. We must make sure we consider all facets of these activities to make participation in this type of trial seamless to the patient and their family.

Regulatory considerations

From a regulatory perspective, country-specific requirements must be assessed from the outset. For example, when subjects are dosed in a country other than their originating country we must understand and be conscious of the requirements of both the originating and dosing nations. Even though there is no IMP and no dosing in the subject's originating country, the regulatory authority may request to review everything related to the IMP. Unless a patient relocates for the full duration of the study, regulatory and ethics approvals will be needed in both the patient's originating country as well as the dosing country.

Also, informed consent forms (ICFs) specific to patient travel and reimbursement are necessary. In the dosing country, regulatory and ethics may require approval for foreign patients to travel to the dosing country. Study documents must be available in the patient's native language, including the dosing country ICF. For both nations, there is shared hospital liability and country-specific insurance requirements.

Patient and family logistics

From a patient and family travel or relocation perspective, there are many points to consider, including travel logistics and relocation assistance. Imagine what must go into uprooting your family to another country or region to participate in a drug development program. There are passport or visa requirements; language barriers; and the need for an interpreter, school support, support for the rest of the family, including financial support, social support, insurance, etc.

Additionally, given the length of gene therapy follow-up requirements, patients and their families will likely go through many changes (i.e., changes with family dynamic, relocation, etc.). Planning for all of these logistics at the outset are imperative for success in these types of trials to attract patients and ensure they remain in the study for the entire trial.

> Gene therapy adds additional complexity to clinical trials given the logistical challenges for specialized therapies, but it also allows for great scientific gains.

Data considerations

Lastly, because patient data will need to be monitored at the originating site as well as the dosing site, different sites will need access to the same patient data; and that access could cross country lines. Collaboration between the dosing center and originating center physicians is imperative to ensure continuity of care and, ultimately, for patient safety. Prior to participating in this type of study, a site must ensure that their data collection capabilities allow for such scenarios.

In summary, gene therapy adds additional complexity to clinical trials given the logistical challenges for specialized therapies, but it also allows for great scientific gains. When embarking on this type of study, we must always prepare for the regulatory intricacies and data needs early on and consider the patients, their caregivers, and their families to ensure that every enrolled patient stays enrolled throughout the entirety of the study.

— Mariah Baltezegar is Executive Director, General Medicine, Syneos Health, and co-leads the company's Health Rare Disease Consortium. She can be reached at mariah.baltezegar@syneoshealth.com.

Monoclonal Antibodies: Clinical Pharmacology Keys

Narine Baririan, PharmD

Outlining the unique pharmacokinetic factors that should be considered when designing and running early stage clinical trials for monoclonal antibodies.

PEER REVIEW

Antibodies, also called immunoglobulins (Igs), are large proteins used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. Several monoclonal antibody (mAbs) drugs have been approved, or are at the late stage of clinical development within various therapeutic indications. The amount of mAbs making it to the market will continue to increase thanks to their characteristics, including good solubility and stability, long persistence in the body, high selectivity and specificity of action, and low risk of toxic metabolites.

However, mAbs still have complex pharmacokinetic (PK) and pharmacodynamic (PD) properties compared to small chemical molecules. These include poor bioavailability, slow distribution, both linear- and non-linear elimination processes, and other factors influencing PK and PD such as immune reactions/immunogenicity.

Before planning a first-in-human (FIH) study, robust preclinical data should be available providing sufficient insight into the full PD pathways, and used to select the most appropriate animal species from both PK/PD and safety considerations. Challenging steps in designing FIH studies with mAb drugs, therefore remain, and the appropriate selection/exclusion criteria of healthy volunteers, a carefully selected safe and appropriate starting dose; the choice of dose escalation steps to achieve the goal of FIH study; the planning of sufficient and correct follow-up procedures; and the safety monitoring necessary, considering both the short term site related reactions and delayed PD effects.

In addition, due to incidents in the past, authorities look more rigorously toward mAbs, considering many of them as high-risk medicinal products. A sound early clinical development plan, including appropriate justifications, might help regulatory bodies with their evaluation of what they view as high risk.

Initial monoclonal antibody drugs were generated from mouse and rat hybridomas, and these first-generation antibodies had only limited clinical success because of their short half-lives and high immunogenicity. Several approaches have been developed to humanize these rodent antibodies, and technological advances during the past four decades have allowed mAbs to be developed and produced at commercial scale. The FDA and the European Medicines Agency (EMA) have approved many mAbs in various therapeutic areas, and it is estimated that several hundred mAbs are currently in development.

Specificities of mAbs

As noted, (PK/PD) analyses are essential steps in the early drug development process. Antibody drugs often exhibit PK/PD properties that are much more complex than those typically associated with small-molecule drugs (i.e., organic compounds with molecular weight <1,000 Da).[1]

Absorption

Most of the marketed antibodies are labeled for intravenous administration, but several mAbs are under development or have been approved for intramuscular or subcutaneous injections. The subcutaneous route is of growing interest as an administrative method, however, factors affecting the bioavailability, such as catabolic first-pass clearance, subcutaneous transport processes, and translation of subcutaneous animal data to humans require further research.[2] Oral administration of mAbs for systemic therapy is not indicated, because of their size, polarity, and gastrointestinal degradation, which preclude adequate bioavailability.[3]

The bioavailability of mAbs after intramuscular or subcutaneous administration varies between 50% and 80%.[4] As a rule, after subcutaneous administration, biologicals

with molecular weight >16kDa are largely absorbed into the lymphatic system (slow absorption rate), while those <2kDa are absorbed into the blood circulation.[3,5] mAbs and their derivative drugs are large biologicals with a molecular weight of around 150kDa; therefore, after intramuscular or subcutaneous injection, absorption of these drugs into the lymphatic system proceeds slowly, and the time to reach maximal plasma concentrations typically ranges from two to eight days.[6]

There is a relatively new interest in the development of aerosolized mAbs for pulmonary delivery, as the lungs have a very large surface area and a high perfusion rate. In addition, pulmonary epithelial cells are known to express neonatal Fc-receptor (FcRn), which may facilitate efficient systemic absorption of antibody delivered to the lung. However, similar to, or even more than, intramuscular or subcutaneous administration, the feasibility of pulmonary delivery of mAbs is limited to those with very high dose potency, as only small volumes of fluid can be administered.[1,4]

Distribution

Analysis of antibody distribution is much more complicated than the analysis of the distribution of most small molecule drugs. mAbs are often designed to bind with high affinity to tissue sites containing the target antigen; however, because of their large size and hydrophilic nature, they have a slow distribution to peripheral tissue.[4] Unlike small molecules, the paracellular movement of biologics is mainly via convective transport instead of passive diffusion.

Higher mAb concentrations have been observed in body tissues that are highly perfused with relatively leaky vascularization such as the spleen, liver, and bone marrow; but very little distribution to the brain. This may be because of the blood-brain barrier with its "tight junctions," the rapid turnover of brain intestinal fluid, or potentially because of the active involvement of the FcRn in mAb efflux from brain tissue.[1]

Experimentally, and by using a physiologically-based PK (PBPK) model, the tissue to blood ratio of mAbs was estimated to be in the range of 0.1 to 0.5, but only 0.02 for the brain.[1,6]

If the target of the mAb is localized in tissue, slow and/or low distribution to tissue from the systemic circulation may be an obstacle to achieving clinical responses. Alternatively, antibody fragments, consisting of only an antigen-binding part (Fab fragments) or single-chain variable fragments, can cross the blood-tissue barrier more easily and, hence, are less hindered by this "binding-site barrier" and poor distribution compared to intact mAbs.[4]

Additionally, for macromolecular protein drugs such as mAbs, it is likely that a significant fraction of drug elimination occurs from tissue sites that are not in rapid equilibrium with plasma. In such situations, non-compartmental analysis of plasma data will lead to an underestimation of the distribution volume (Vd). When significant drug elimination occurs from "peripheral compartments," it is not possible to obtain precise estimates of Vd from analysis of plasma data alone. Plasma concentrations may be used to define the range of possible values for the distribution volume, but the determination of tissue concentration by biopsies or imaging techniques would provide more insight into distribution.[6]

Elimination

Because of their molecular size, mAbs are not generally excreted into urine, but are metabolized to peptides and amino acids that can be reused in the body for the de novo synthesis of proteins, or are excreted by the kidney. A few mAbs with a molecular weight <69 kDa are mainly cleared by renal excretion, and thus the clearance of these biologics can be compromised in patients with renal impairment.[3] Several elimination mechanisms are reported to be involved in mAbs elimination, of which the three most commonly observed are proteolysis by the liver and the reticuloendothelial system, target-mediated elimination, and nonspecific endocytosis.

First, phagocytic cells such as macrophages and monocytes are expected to play a role in the elimination of mAbs, as they are also key factors in the elimination of endogenous IgG. Internalization and subsequent degradation of IgG by lysosomes in these cells occurs predominantly after binding of the Fc part of the antibody to Fcg-receptors expressed on these cells.[4]

A second elimination route is degradation of the mAb within the target cell after internalization and subsequent intracellular degradation in its lysosomes. For mAbs targeting an antigen located on cells, degradation by target cells after binding of the Fv-part to the target antigen (target-mediated elimination) is probably the most important elimination route. As this route is saturable as a result of the confined amount of target antigen, non-linear elimination has often been reported for mAbs.[3] The rate of uptake and elimination of antibodies by target-mediated pathways is a function of dose, the expression level of the target, the kinetics of receptor internalization, and intracellular catabolism.[1]

Finally, mAbs may also be taken up into cells in different tissues by non-specific pino- or endocytosis. After uptake in the slightly acidic environment of the endosomes in endothelial cells, the immunoglobulins bind to the FcRn. After binding, the IgG-FcRn complex is transported back to the cell surface, where it is released again into the circulation. In contrast, unbound IgG is degraded into amino acids by lysosomes present in the cell.[4] In the absence of target-mediated drug clearance, most IgG-based mAbs exhibit long half-lives, typically three or four weeks, mainly as a result of FcRn-mediated antibody recycling.[3]

Another distinction between small molecules and biologics is that biologics can be immunogenic, leading to the formation of neutralizing anti-drug antibodies (ADA). It has been shown that the change in elimination rates resulting from immunogenicity may be either increased or decreased, depending on the number of sites on the therapeutic mAb that the endogenous anti-mAb are directed against. Because of individual differences in the immune response to mAb administration, it is difficult to predict how immune response influences the elimination rate of therapeutic mAbs and whether a change in the elimination rate has clinical implications.[3] The degree of humanization, route of administration, duration of therapy, and dose level can also impact immunogenicity.[3]

A complication with any ADA response found in preclinical species is that it does not accurately predict the ADA response in humans. Therefore, it is essential to assess the ADA response in FIH studies and evaluate this information with respect to its impact on PK and/or PD, when possible. If there is an effect on PK (and related to that to PD), it is frequently that the elimination of the affected mAb drug is increased, resulting in a reduced systemic exposure; this additional clearance pathway should be considered when establishing a PK or PK/PD model, and when designing the further clinical evaluation studies.[9,10]

Designing FIH studies for mAbs

Since the 1980s, mAbs are increasingly being incorporated into clinical practice as therapeutic options, particularly in oncology and immunology, and several are still under development. While these targeted therapies are predicted to be highly selective and specific, protein-based drugs such as mAbs, like all drugs, can have unpredictable safety profiles.

One of the reasons for the revised EMA guidance released in 2007 was a FIH trial in 2006 with a new mAb drug.[11] All subjects receiving the first dose of active drug TGN1412, a superagonist mAb against CD28, developed a life-threatening, severe adverse reaction, caused by an uncontrollable cytokine release. The maximum recommended starting dose (MRSD) was, nevertheless, determined by the conventional allometric approach from the no-observed adverse effect level (NOAEL) with a large safety factor of 160, resulting in 0.1 mg/kg. However, when using the receptor occupancy to reinvestigate this dose, it was found that 0.1 mg/kg would elicit greater than 90% receptor occupancy. So, in this situation, not only was the pharmacodynamic effect unacceptably high, producing a cytokine storm, the increased receptor occupancy could also have altered the pharmacokinetics of the antibody by decreasing its clearance, thereby further increasing the peak concentration and prolonging its effect.[12,13]

This tragic incident highlighted the importance of, and difficulties in, selecting the safest MRSD in FIH studies with mAbs. One of the lessons learned from this tragedy is that once receptor occupancy starts to increase, the PD and PK response to further dose escalations becomes non-linear. The TGN1412 incident led to the recommendation that the MRSD should also be calculated based on the minimal anticipated biological effect level (MABEL). It is important to determine in preclinical studies whether target-mediated elimination occurs, which should be considered when deriving the MABEL.

MABEL is useful for protein drugs because it defines a dose at which receptor occupancy is low. Per the revised EMA guideline, the FIH doses need to be calculated from both NOAEL and MABEL, and the lowest value is recommended for the clinical trial.[14] For biotherapeutics, such as mAbs, with potential agonistic modes of action on key body systems, no more than 10% receptor occupancy is proposed as starting dose in a FIH trial.[15] For mAbs with antagonistic actions, a higher receptor occupancy is needed for a pharmacological effect, and, therefore, a starting dose inducing higher than 10% occupancy may be acceptable. Importantly, the selected starting dose for a FIH trial, as well as the desirable highest pharmacological active doses, should be justified, considering target saturation by mAbs and systemic PK behavior.

Also, according to the draft EMA guideline published in 2016, specific attention should be paid to the preclinical development program of mAb drugs as a support to FIH studies.[16] Data on the functionality of additional antibody domains in animals should be present; for example, the Fc receptor. The demonstration of pharmacological relevance of the animal model(s) for the mAbs under development is crucial, and may include comparison with humans via tissue cross-reactivity studies using human and animal tissues.

Suh and colleagues published a review article in 2016 covering the results of FIH studies with mAbs from 1990 to 2013, with access to the starting dose estimation.[13] The NOAEL-based approach was still the most commonly used MRSD determination method for FIH studies with mAbs (21.5%). The publication year was significantly associated with the choice of MRSD determination method. The proportion of FIH studies that did not report the MRSD determination method was very high, at more than 50%, in 1990-2007, while the MABEL-based approaches were more frequently used in 2011–2013, with an incidence of more than 30%. The increase in adoption of MABEL for the more recent studies reflects the impact of the TGN1412 incident and the EMA guideline that followed. Although the MABEL-based approach produced an MRSD lower than those derived by the other approaches, the average number of dose escalation steps was similar.

Many mAbs are intended to treat different oncological pathologies, and, therefore, FIH studies in that indication may have some other particularities. The one-sixth highest non-severely toxic dose has been introduced as an alternative method in estimating MRSD, not resulting in unacceptable toxicities in FIH (not exceeding the maximum-tolerated dose) and reducing dose escalation steps.[17] Independent of the safety profiles of mAbs, once the oncological indication is obvious, the FIH may be performed in patients rather than in healthy volunteers, as a treatment option in the absence of an effective alternative treatment. Consequently, the challenge to avoid the under-dosing of patients is added to the starting dose estimation and dose escalation determination process.[13,17]

Another challenge when developing a mAb is determining the optimal route of administration. Site reactions are a common side-effect of antibodies when administered subcutaneously or per infusion and can lead to interruption and termination of a FIH study. The implementation of prophylactic measurements such as H1- and H2-blockers, steroids, paracetamol, and the prolongation of the infusion might help to avoid reactions. Any implementation of such measures in early phase trials substantially influences the further development of the compound.[18] The best approach would, therefore, be to foresee a continuous observation of patients during the first hours after the injection of new mAb with a well-established treatment schema in an experienced clinical pharmacology unit.

Another factor that should be taken into account when designing the FIH trial of mAb drugs is the possible delayed PD effect related to duration of target inhibition or target-mediated PK profile. Sufficiently long follow-up of subjects should be foreseen to monitor possible delayed adverse reactions. Human terminal elimination half-life predicted by modeling and simulation (M&S) and/or by using physiologically-based PK (PBPK) modeling may support the estimation of the duration of the long-term follow-up period in trials with mAbs administered as single or multiple doses in early phases.

If we follow the EMA draft guideline (2007),[19] "Medicinal products are defined as potential high-risk medicinal products when there are concerns that serious adverse reactions in FIH clinical trials may occur." In the recent EMA guidance for FIH trials (2017), "the potential risks that might arise" during the FIH studies with any new compound and "appropriate risk mitigation strategies" are discussed without highlighting the "high-risk" compounds class.[14] Even if mAbs are in clinical research for more than 30 years, they are often still considered high risk because of uncertainties regarding the mode of action, the nature of the target, and/or the relevance of animal models. However, this is not always the case, for example, when:

- The mAb mechanism of action is fully investigated with primary and secondary targets.

- Target-mediated elimination is of minor role.
- Particularly linear PK/PD is observed.
- A mAb drug is on the market with similar physicochemical and PK/PD properties.
- Advanced modeling and simulation (M&S) is assisting all the steps of preclinical and clinical development.

Regulatory agencies and research ethics committees rightly insist on the use of a "sentinel" group approach in FIH, particularly in the single dose part, comprising one active-treated and one placebo-treated subject at the start of the study, and at each dose increment. This approach is mandatory in non-standard situations, such as when drugs are first-in-class, if their anticipated physiological effects are potentially profound, and when non-linearity in PK/PD is suspected. This is likely to apply for most mAbs. The intention is to identify any highly repeatable serious adverse event in a single subject rather than being faced with an entire cohort in trouble, as happened in the TGN1412 trial.[20] Which data to analyze from the sentinel group, the time needed to observe them before proceeding, staggered dosing, and whether this should be done in every escalation step are further challenges that will need to be solved by clinical and PK/PD experts.

Additionally, there are certain data which need to be reviewed on a case-by-case basis, such as the individual mAb drug properties, any available preclinical safety and PK/PD data, and the subject population. After each sentinel group, a safety review committee, or more complete data monitoring committee (including PK, PD, and other available data review) may be required. The added value of reviewing the PK and PD data at interim stages will depend on the individual mAb PK/PD profile—assessing among other things, the mechanism of action, drug half-life, and target-mediated distribution and elimination. The same review approach is applicable during dose escalation and decision-making steps in a FIH studies with mAb drugs.

Conclusion

The PK and PD of mAbs are complex and differ from those of non-mAb drugs. There are numerous PK factors that should be taken into account when designing and running an early phase clinical trial, especially if an antibody has a novel mechanism of action. The growing shift from NOAEL to MABEL, in particular, has the potential to reduce the risks to trial subjects being dosed with a novel mAb for the first time. Careful trial design, informed by knowledge of an antibody's PK peculiarities, is essential if the study is to run both smoothly and safely.

References

1. W Wang, EQ Wang and JP Balthasar; Monoclonal antibody pharmacokinetics and pharmacodynamics, *Clin Pharmacol Ther*, Nov 2008, 84(5): 548-558
2. Wolfgang F. Richter, Suraj G. Bhansali and Marilyn E. Morris; Mechanistic Determinants of Biotherapeutics Absorption Following SC Administration, *The AAPS Journal,* Sep 2012, 14, (14)3: 559-570
3. Liang Zhao, Tian-hua Ren, Diane D Wanf; Clinical pharmacology considerations in biologics development, *Acta Pharmacologica Sinica*, 2012, 33: 1339–1347
4. Ron J. Keizer, Alwin D.R. Huitema, Jan H.M. Schellens and Jos H. Beijnen; Clinical Pharmacokinetics of Therapeutic Monoclonal Antibodies, *Clin Pharmacokinet*, 2010; 49(8): 493-507
5. Tang L, Meibohm B; Pharmacokinetics of peptides and proteins. Pharmacokinetics and pharmacodynamics of biotech drugs. Weinheim: Wiley-VCH Verlag GmbH and Co, 2006: 17-43
6. Lobo, E.D., Hansen, R.J. and Balthasar, J.P; Antibody pharmacokinetics and pharmacodynamics. *J. Pharm. Sci.*, 2004, 93, 2645–2668
7. Liming Liu; Pharmacokinetics of monoclonal antibodies and Fc-fusion proteins; *Protein Cell*, 2018, 9(1): 15–32
8. Josiah T. Ryman and Bernd Meibohm; Pharmacokinetics of Monoclonal Antibodies; *CPT Pharmacometrics Syst. Pharmacol*, 2017, 6, 576–588
9. Guideline on Immunogenicity assessment of therapeutic proteins; May 18, 2017; EMEA/CHMP/BMWP/14327/2006 Rev 1
10. Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products; July 19, 2007; EMEA/CHMP/SWP/28367/07
11. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products; July 20, 2017; EMEA/CHMP/SWP/28367/07 Rev. 1
12. Vijay Sharma and John H McNeill; To scale or not to scale: the principles of dose extrapolation; *British Journal of Pharmacology*, 2009, 157, 907–921
13. Hoon Young Suh, Carl CPeck, Kyung-Sang Yu, Howard Lee; Determination of the starting dose in the first-in-human clinical trials with monoclonal antibodies: a systematic review of papers published between 1990 and 2013; *Drug Design, Development and Therapy*, 2016, 10, 4005–4016
14. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products; July 20, 2017; EMEA/CHMP/SWP/28367/07 Rev. 1
15. Zou P, Yu Y, Zheng N, Yang Y, Paholak HJ, Yu LX, Sun D; Applications of human pharmacokinetic prediction in first-in-human dose estimation; *AAPS J.*, 2012, Jun;14(2):262-81
16. Guideline on development, production, characterisation and specification for monoclonal antibodies and related products; July 21, 2016; EMA/CHMP/BWP/532517/2008
17. Aaron R. Hansen et al; Choice of Starting Dose for Biopharmaceuticals in First-in-Human Phase I Cancer Clinical Trials; *Oncologist*, 2015, Jun; 20(6): 653–659
18. Adrian M. Senderowicz; Information Needed to Conduct First-in-Human Oncology Trials in the United States: A View from a Former FDA Medical Reviewer; www.aacrjournals.org, published online first March 9, 2010; DOI: 10.1158/1078-0432.CCR-09-2766
19. Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products; March 22, 2007; EMEA/CHMP/SWP/28367/2007 Corr.
20. J. M. Ritter; More on first-in-man studies; *Br J Clin Pharmacol*, Nov 5, 2010, 70(5): 629–630

Narine Baririan, *PharmD, is Clinical Pharmacology and PK Expert, SGS - Clinical Research*

Models of Engagement: Patients as Partners in Clinical Research

Lindsay Singler, Patty McAdams, Gina Uhlenbrauck, Kirk Jernigan, Julie Schulman

Exploring three distinct patient partnership models to help researchers assess which methods of engagement could work best for their clinical programs.

PEER REVIEW

As patients take more active roles in decision-making about health, healthcare, clinical trials, and regulatory activities, their influence has changed how sponsors and researchers view patient involvement in clinical research. Once regarded as "subjects" who had research performed on them, patients are now contributing across the spectrum of clinical development, including in the design and planning of research protocols, selection of outcomes and endpoints, development of recruitment and retention strategies, and dissemination of research results. The unique perspectives afforded by patients' lived experiences can inform researchers' approaches and help identify knowledge gaps. By sharing their experiences of the daily burden of disease and their perspectives regarding unmet needs, therapeutic burdens, the balance of benefit and risk, and the types of research questions most important to them, patient partners can transform the clinical development process from one directed by sponsors and investigators to one driven by the needs of patients and their caregivers.

While the concept of patients as partners in clinical research is gaining momentum, recent research points to room for improvement.[1] The development and validation of partnership models to engage patients in the design and governance of clinical research programs is still in its infancy, and approaches that can ensure meaningful and effective patient participation in research are needed.[2] For this reason, the Duke Clinical Research Institute (DCRI) and our research partners are exploring models of patient engagement to determine what works best for patients, their caregivers, research sponsors, and investigators, with the ultimate goal of enhancing the speed and quality of clinical research.

In this article, we describe three different patient partnership models to help researchers evaluate which method of engagement could work best for their clinical program or study. These models integrate patients and their caregivers into the governance structure of the clinical research program or study to ensure continuous partnership throughout the project life cycle. The models of patient engagement and studies profiled include:

- Patients as advisory board members: the ADAPTABLE aspirin study and CONNECT-HF trial
- Patients as steering committee members: Industry-sponsored Phase II study
- Patients as co-investigators: the PCORnet obesity studies

We discuss these models, the methods used to implement them, and outcomes to date. We also share lessons learned and explore future possibilities for patient engagement in clinical research. This paper is written from the perspective of communication professionals who work alongside research sponsors and study teams—including faculty, operations staff, researchers, clinicians, and patient advisors—to facilitate patients as partners in clinical research. We fully recognize that a commitment from all parties, including our patient partners, is necessary to a successful, lasting engagement.

PCORnet: The ADAPTABLE aspirin study

PCORnet (the National Patient-Centered Clinical Research Network) is an initiative funded by the Patient-Centered Outcomes Research Institute and is designed to build patient partnerships and harness health data to improve clinical research. PCORnet ensures that patients are directly involved in the development and execution of research by weaving requirements for patient involvement directly into the network's governance structure. Patient members

are represented on each of the overarching PCORnet governing committees where they play an integral role in overseeing decision-making and leadership, stakeholder engagement, PCORnet's data network, and research partnerships.

The DCRI serves as the coordinating center for PCORnet and also leads its first demonstration project, ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness; NCT02697916). A pragmatic clinical trial designed to answer an important clinical question in the "real-world" setting of patient care, ADAPTABLE is comparing the effectiveness and safety of two different daily doses of aspirin, both of which are widely used for secondary prevention of heart attack and stroke in persons living with heart disease. However, the study is also implementing a new model of patient engagement in clinical research by integrating patient partners, known as the "Adaptors," into the study team to provide patient voices and perspectives in all aspects of the trial. The Adaptors team is facilitated by Health eHeart Alliance, a PCORnet Patient-Powered Research Network.

Eight PCORnet Clinical Data Research Networks (CDRNs) and a Health Plan Research Network are involved in the identification and recruitment of study participants. At the onset of the study, each CDRN invited a patient to join the Adaptors team. Some Adaptors have previous clinical research experience through personal or professional experiences; all consider themselves healthcare experts through their lived experiences battling chronic diseases.

Optimizing the recruitment message

By participating in ongoing study meetings, Adaptors hear firsthand about recruitment challenges and barriers to enrolling up to 15,000 patients in the ADAPTABLE study. Working with their local network researchers, Adaptors play a key role in tailoring the recruitment messages (see Table 1). Adaptors help develop and review recruitment materials, anticipating questions and identifying potential points of confusion. They offer input on study materials that facilitates understanding and enhances appeal to a broad audience, such as incorporating graphics and white space, reducing jargon and legalese, and using language that emphasizes the importance of clinical trials, the role of patients in the process, and the value of the patient voice in transforming healthcare. Adaptors have also contributed as authors in peer-reviewed literature.[3]

Scope of Support
Help design the consent form, protocol, and study portal.
Assist in developing, reviewing, and providing feedback on study materials, such as participant brochures and letters.
Participate in conferences and investigator, steering committee, and working group meetings.
Publish, blog, present, and talk about their engagement experiences in ADAPTABLE.
Share relevant news on social media.
Develop plain-language summaries to share study updates and results.

Source: Singler et al.

Table 1. ADAPTABLE patient partners engagement activities.

Better health outcomes for all when patients partner with researchers

In addition to spreading awareness of ADAPTABLE, Adaptors are dedicated to educating others on the importance of clinical research. Their motto, "Better health outcomes for all when patients partner with researchers," conveys how patient participation can help answer health questions that matter most to patients and their doctors. This motto is part of the Hero's Journey Art Project, a touring art exhibit developed by Eli Lilly to honor trial participants and raise awareness of clinical research.

> Once regarded as "subjects" who had research performed on them, patients are now contributing across the spectrum of clinical development, including in the design and planning of research protocols.

Through the ADAPTABLE patient-research partnership, patient partners have come to appreciate how their experiences can inform research questions, protocol design, and the collection of patient-reported outcomes (PROs). Researchers have come to understand that patients may have their own perspectives on what study outcomes or endpoints are most important. For example: an investigator might assume that the most important question to ask during a therapeutic trial is whether the intervention results in an improvement in mortality. However, a patient might be more concerned with quality-of-life issues—if they experience a stroke, will they have to live with a disability, and what will the impact on their family be?

The CONNECT-HF trial

The Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure (CONNECT-HF; NCT03035474) is a nationwide pragmatic clinical trial funded by Novartis and coordinated by the DCRI. CONNECT-HF employs digital and quality improvement approaches to enhance care for patients with heart failure, with the goal of improving outcomes and reducing the number of hospital readmissions. The CONNECT-HF trial team worked closely with a team of patient advisers while designing the study. To establish the patient advisory group, physicians on the trial steering committee were asked to nominate patients from their practices who they felt would be engaged and interested in giving back to help others with heart failure. Although there were no official requirements for selection, the team aimed to identify advisers who had similar characteristics to the expected trial population, including a similar degree of diversity with regard to age, sex, race/ethnicity, and geographical location.

The resulting group of eight patient advisers—the "Cardi-Yacks"—were not professional patient advocates, and most had never partic-

ipated in a clinical trial. A DCRI patient engagement liaison facilitated interactions between the trial team and the Cardi-Yacks by orienting them to their roles, outlining expectations, answering questions, scheduling meetings, and conveying requests for input from the trial team. The Cardi-Yacks, in turn, offered their experiences and advice on aspects such as eligibility criteria and the follow-up phone call schedule to help researchers design a trial that would be both useful for patients and easy for them to participate in.

An in-person meeting was organized for the Cardi-Yacks at the trial coordinating center, where they met with the project team and gave feedback on the trial enrollment process and patient-facing educational materials. The meeting included individual mock enrollment sessions with each Cardi-Yack to replicate the patient experience of enrollment. The Cardi-Yacks then participated in a facilitated focus group to provide input on the enrollment process and draft patient-facing materials that would make them more useful and patient-friendly. In addition, the Cardi-Yacks piloted patient-facing mobile applications that are part of the trial interventions and gave input directly to the application designers. The Cardi-Yacks expressed positive feelings about being partners in the trial and helping others with heart failure through their involvement. After trial enrollment began, the Cardi-Yacks continued to work with the trial team on recruitment, adherence, and retention.

Search Profile
SELECTION MODEL STEPS
Confirm sponsor's objectives for including patient representative on steering committee.
Develop ideal profile and nomination form for patient representative.
Each steering committee member (including sponsor) nominates one patient representative.
Steering committee votes on nominees to create short list of two to three most eligible candidates.
Contact short-listed persons to assess interest in role.
Sponsor makes final decision on selection of patient representative.
Sponsor, DCRI, and steering committee appoint patient representative.
In collaboration with steering committee and sponsor, DCRI develops and implements plan to support, train, empower, and engage appointed patient representative.
PATIENT REPRESENTATIVE'S ROLE
Provide input on study protocols and protocol amendments (with particular reference to PRO endpoints), anticipated participant experience, and study burden.
Give feedback on: • Conduct of studies in terms of how patient comfort and convenience can be optimized within constraints of protocol requirements. • Model informed consent form. • Participant recruitment and retention tactics, including review of draft recruitment and retention materials.
Contribute to plan for public dissemination of study findings, e.g., a return of results document summarizing data for public

Source: Singler et al.

Table 2. Patient representative selection and role.

Industry-sponsored Phase II study

DCRI is spearheading an engagement initiative for a patient to serve as a member of a Phase II study's steering committee. The selected individual would give input on protocol design, anticipated burden for study participants, recruitment and retention tactics, and other key areas. DCRI would be responsible for the engagement and education of this patient representative, whose views would carry as much weight as those of other steering committee members.

Internal selection process

The DCRI team, working in close collaboration with the principal investigators and other study stakeholders, has developed a customized internal process according to the therapeutic area, patient population, and protocol (see Table 2). This customized process enabled us to establish a profile for an "ideal" patient representative, develop selection criteria, identify potentially suitable candidates, and clearly define the role of nominated persons.

Value to patients and research

While this patient engagement initiative is still in the early stages of the nomination process, the DCRI is optimistic about the benefits the patient representative could bring to the study. The study team believes this additional layer of patient engagement could strengthen partnerships between patients and study staff, demonstrating the value of patients' viewpoints in clinical research. It could also facilitate effective communication between the patient representative and the steering committee members.

PCORnet obesity studies

In addition to the ADAPTABLE aspirin study, PCORnet is also conducting a pair of observational studies on obesity. Like many PCORnet demonstration projects, these studies require a patient or caregiver to be included as a co-principal investigator (PI).

The Antibiotics and Childhood Obesity Study, led by Harvard Pilgrim Health Care, examines the relationship between antibiotic use in the first two years of life and weight gain in later childhood. The parent co-PI for the study is a special education teacher and the parent of a teenage son who has experienced childhood obesity for most of his life. As a co-PI, he oversees patient engagement efforts and works to address potential barriers to patient involvement by openly discussing concerns about data security and anonymity and by creating a patient- and family-friendly glossary of acronyms commonly used within the medical community.

A patient co-PI for PCORnet's Bariatric Study, led by Kaiser Permanente Washington Health Research Institute, is building evidence on which of three different bariatric surgical procedures results in the best outcomes for specific patient communities. A church pastor, community advocate, and bariatric surgery patient herself, the patient co-PI shares her story, "Why patients need a louder voice in medical

research," which explores her experience of being part of an underrepresented patient community seeking bariatric surgery, the knowledge gaps that exist in the current medical literature, and the importance of patient partnership in clinical research.

The PCORnet obesity study co-PIs have built strong collaborations between patients, clinicians, and healthcare system leaders. One of the unifying messages shared by both co-PIs is how they have learned that these partnerships benefit not just patients but all stakeholders—everybody wins. The model has demonstrated the power of patients' unique voices when they are thoughtfully integrated into the fabric of decision-making and governance. PCORnet and the DCRI plan to continue to share news on patient engagement strategies, best practices, and lessons learned, highlighting personal stories from throughout the PCORnet partner networks and studies.

The future of patient engagement in research

The DCRI has been exploring approaches to patient engagement for some time. Large-scale initiatives with DCRI involvement, such as PCORnet, have been characterized by extensive partnerships with communities and individuals to shape, inform, and improve research design and conduct.

In June 2017, the DCRI appointed Bray Patrick-Lake, MFS, as director of stakeholder engagement. A former trial participant who later became a patient advocate, Patrick-Lake led a multi-stakeholder team of experts from industry, academia, patient groups, the NIH, and the FDA to develop best practices for effective engagement with patient groups around clinical studies for the Clinical Trials Transformation Initiative (CTTI). She also developed successful patient engagement models and strategies for PCORnet studies, co-chaired the Advisory Committee to the NIH Director responsible for authoring the vision of the Precision Medicine Initiative Cohort Program (now called *All of Us*), and served as the interim director of engagement during the program's pilot phase. Under her leadership, DCRI faculty, investigators, and operational teams are working to institutionalize a set of guiding principles for involving patients as partners in clinical research (see Table 3).

Engagement Expectations
1. People come first. Always.
2. We recognize that people are embedded in dynamic family and community frameworks that we honor and respect across the continuum of life care.
3. People are our partners in research, not our subjects. We believe in taking every opportunity to co-learn. We engage patients, families, and community members in our research design, conduct, oversight, and dissemination activities.
4. We are transparent and trustworthy. We communicate to research participants how valuable their contributions are to science and medicine. We take the time to thank research participants, update them on progress, and share our findings in language understandable to everyone.
5. We create value. We work to return results in a responsible and meaningful manner and maximize what can be learned by sharing data with other researchers.
6. We give back. We are not transactional in our approach. We encourage and incentivize collaborations with people and communities that look past the end of a project or last study visit. We create opportunities to continue co-learning and working in partnership with patients, families, and community members to improve health outcomes.

Source: Singler et al.

Table 3. DCRI core principles for patient engagement.

The DCRI is working to catalyze the adoption of a gold standard of partnership with patients in research design, conduct, oversight, and dissemination, while raising the bar on participant experience in research. Although including patients in the governance of clinical studies is just one approach to advancing patient partnerships in clinical research, we have found it to be an effective tool for supporting high-quality, efficient, patient-centered research. Patient input in clinical research has many potential benefits, such as making it possible to achieve higher rates of retention and compliance through enhanced value and improved participant experience; improving data quality by minimizing patient dropout and enhancing participant adherence to protocol; and inspiring scientists to pursue research opportunities and approaches that might not have been obvious.

Finally, we anticipate that continuous patient input could drive more rapid research innovation cycles and accelerate the development and appropriate scaling of novel methods and tools. Effectively integrating patient partners into clinical research requires thoughtful approaches and bidirectional learning. Their participation throughout the clinical development life cycle is proving invaluable to improving clinical studies and forging new paths in biomedical research.

References

1. Calaprice-Whitty D, Byrne J, Gilbert J. Bridging the gap for better patient engagement. *Applied Clinical Trials*. May 31, 2017. Available at: http://www.appliedclinicaltrialsonline.com/bridging-gap-better-patient-engagement [20]. Accessed Oct. 13, 2017.
2. Domecq JP, Prutsky G, Elraiyah T, et al. Patient engagement in research: a systematic review. *BMC Health Serv Res*. Feb. 26, 2014;14:89.
3. Hernandez AF, Cruz HP. Engagement, research, and evidence: Leveraging the National Patient-Centered Clinical Research Network for better cardiovascular health. *Circulation*. 2017;135(16):1478-1480.

Lindsay Singler *is Associate Director, Clinical Research Communications;* ***Patty McAdams*** *is Clinical Research Communications Specialist;* ***Gina Uhlenbrauck*** *is Clinical Research Communications Manager;* ***Kirk Jernigan*** *is Clinical Research Communications Specialist;* ***Julie Schulman*** *is Clinical Research Communications Specialist, all with Duke Clinical Research Institute (DCRI)*

* The authors would like to acknowledge the following individuals for their leadership in implementing the models of engagement profiled in this paper: Adrian F. Hernandez, MD, MHS; Matthew T. Roe, MD, MHS; William Schuyler Jones, MD; Holly Robertson, PhD; Madelaine Faulkner, MPH; the Adaptors; Jane Anau, BS; David Arterburn, MD, MPH; Jason Block, MD, MPH; Doug Lunsford; Juliane Reynolds, MPH; Neely Williams; Beth Martinez, PMP; Adam DeVore, MD; Linda Davidson-Ray; Tracy Hofmann; Renee Leverty; the Cardi-Yacks; and Susan Landis.

Enrollment Cycle Times Can and Should Be Optimized

Valerie Legagneur, Jonathan Peachey, Karen Correa, PhD, Gen Li, PhD

Case study demonstrates that site activation is a key driver in determining patient enrollment cycle time.

PEER REVIEW

Planning clinical trials is challenging. A significant portion of clinical studies cost more than $100 million each and last several years. By any standard, this is a major capital investment, requiring extensive planning. The complexity of conducting a clinical trial is not only reflected by a huge number of variables from the operations management point of view, but also the fundamental reality that these clinical studies are medical and scientific experiments. The questions for a clinical trial planner to answer are often in conjunction with those in operations management and medical development.

While clinical trial planning has been a weak spot for our industry, it is encouraging that many leaders have recognized the importance of planning properly, evidenced by the creation of dedicated clinical trial planning groups, often known as feasibility groups. However, there has been limited progress: delays are still a chronic symptom, costs are ballooning, and rescue missions are a regular part of the trial process. The challenges facing clinical trial planners remain the lack of data and, more importantly, the lack of a platform to interpret the data.

We recognized that there was no easy fix to these challenges. Over the past 10 years, along with building an extensive and dynamic clinical development database, a set of innovative and coherent concepts has been created to help us to interpret the data, to enable us to effectively plan clinical trials.[1, 2, 3, 4, 5]

In this article, we use a hematology clinical trial as an example to illustrate how the PhESi clinical trial planning platform was utilized to aid the clinical trial team and facilitate the communication between the team and key stakeholders, namely the senior management.

The study team faced a familiar scenario: a promising drug candidate, high expectations, demanding timelines, and limited indication experience. This hematological clinical trial would be the first, large-scale, randomized clinical trial for this indication.

Methods

The PhESi platform takes an integrated approach in clinical trial planning. We assess the competitor landscape, including where and when the planned clinical trial will be conducted. Business processes, especially site activation processes,[3] are examined in multiple dimensions. Trial design, specifically patient inclusion/exclusion criteria, is comparatively analyzed against similar trials conducted by the industry, by focusing on how these design elements can potentially impact planning parameters and operational deliverables. Last but not least, all the participating investigator sites in relevant clinical trials are assessed by going through a series of proprietary algorithms and statistical models.[2,4] Those that pass this vigorous selection process are provided to the team as site candidates for the trial being planned.

It is important to emphasize that while our analysis is structured and systematic, not all the detailed results are presented to the team. We focus on providing a set of actionable recommendations the team can act on, substantiated by our analysis, and specific to the particular clinical trial being planned.

Briefly, the team was asked to conduct a hematology clinical trial, targeting enrollment of 292 patients. The sponsor was hoping to complete enrollment in 22 months.

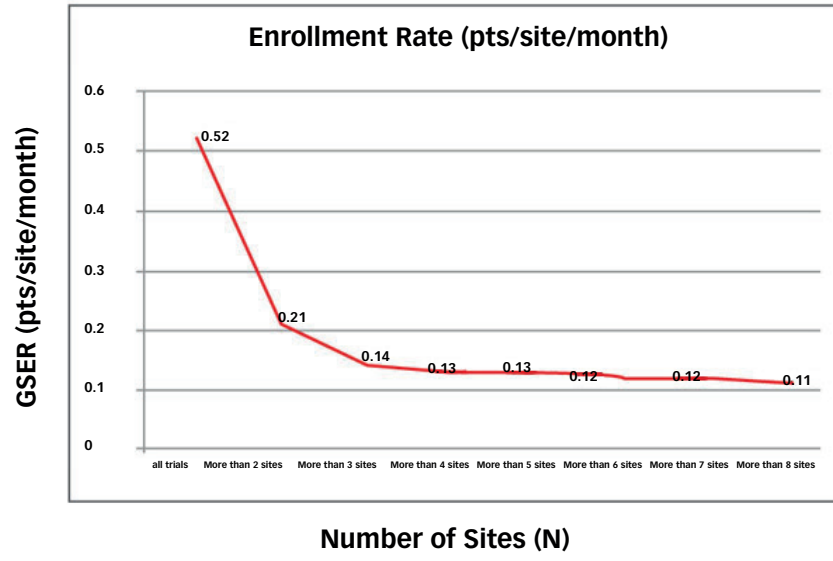
There was a limited number of randomized clinical trials similar to our hematology trial. Simply using historical data for our planning was not possible. Extensive

historical clinical trial data analysis has revealed that there is a reliable pattern between number of investigator sites (N) being deployed in a clinical trial, and gross site enrollment rate (GSER, defined as the number of patients per site per month). That pattern, with minor modification, can be established for trials in this hematology indication[1, 5] (see Figure 1).

Clearly, for a trial that planned to use over 100 sites, it was not realistic to expect an enrollment rate of more than 0.11 patients per site per month. However, as a mathematical relationship can tell us, the GSER could drop below 0.10 patients per site per month, though not significantly.

Figure 2 (see page 34) summarizes the distribution of site size for clinical trials in this hematology indication completed in the past 10 years or so, as measured by the number of patients per site. It is clear that most of the hematology clinical trial sites enrolled one to three patients on average.

Site Volume vs. Enrollment



Source: Legagneur et al.

Figure 1. The pattern established in the hematology trial.

The median number of patients per site for trials is 3.0. Knowing that enrollment rate decreases as the number of sites increases, we need to add more sites than the median number of patients per site implies, which requires about 100 sites to enroll 292 patients. Considering these factors, we recommended that the team should use 120 sites, with expected enrollment of 2.4 patients per site.

One question commonly asked is whether we can proportionally reduce enrollment cycle time by proportionally adding more sites to the mix? The simple answer is no. Among many other reasons, there are operational boundaries in terms of how many sites we can activate that would contribute to enrollment. For a randomized interventional trial targeted to enroll a defined number of patients, we can expect to see an initial shortening of enrollment cycle time when adding sites. As we continue to add more sites, the benefit decreases, eventually resulting in prolonged enrollment cycle time when an excessive number of sites were added to the mix.[1,4] Empirically, we can consistently identify the optimized area (sweet spot), where an adequate number of investigator sites can help us to achieve the shortest enrollment cycle time.[1,4]

In planning our trial here, we had to define the optimized number of sites with similar logic, since we could not calculate that "sweet spot" empirically without sufficient historical data.

Now let us focus on site activation. We examined over 1,000 interventional clinical trials conducted by the sponsor of our trial with 10 or more active sites. We found that only 6% of these studies were able to activate 50 or more sites 100 days after the start date. When we focus on the trials required to activate more than 50 sites, 20% of the trials were able to activate more than 50 sites in the first 100 days. As depicted in Figure 3 (see page 34), even if we put more resources into the larger trials that require a larger number of the sites to be activated, the percentage of trials that can activate 50 or more sites in 100 days plateaued at 25% to 27%.

In other words, only a small percentage (~25%) of large-scale trials can activate 50 sites in 100 days—it is, therefore, an overly ambitious performance goal.

> The complexity of conducting a clinical trial is not only reflected by a huge number of variables from the operations management point of view, but also the fundamental reality that these studies are medical and scientific experiments.

Is it feasible to enroll 292 patients in 22 months, when using 120 sites?

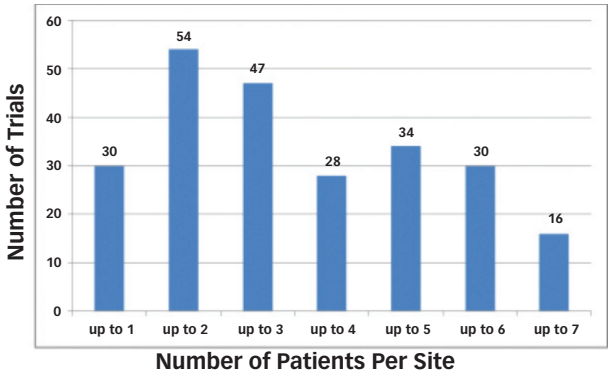
We learned from historical sponsor and industry data that it would take an extraordinary effort to activate 50 sites in the first 100 days. From our analysis, it usually took even longer to activate the next 50 sites. If everything played out to our favor, we would be able to activate 120 sites in nine months (270 days). In those nine months, we could expect to have 60 sites open and enrolling patients on average (assuming a straight site activation curve between month one and month nine). We only had 13 months to fully utilize

the enrollment capacity from all the 120 activated sites. In summary, we would only be able to utilize 80% of enrollment capacity from the 120 sites deployed [(50% x 9 months + 100% x 13 months)/ 22 months]. That 80% is referred to as the Site Effectiveness Index (SEI), which measures the success of the site activation process.[2, 4]

This required us to enroll 0.138 patients per site per month. This enrollment rate was still 26% higher than the historical enrollment rate of these much smaller hematology clinical trials [(0.138/0.11-1)]. Neither an SEI of 80%, nor an adjusted site enrollment rate (ASER) of 0.138 patients per site per month was obtainable.

ASER, which is the GSER when we assume all the sites can be activated in day 1 of the trial. Mathematically, GSER equals to ASER times SEI. For a given protocol, ASER can be improved through a better site selection process.[2,4]

Site Reach



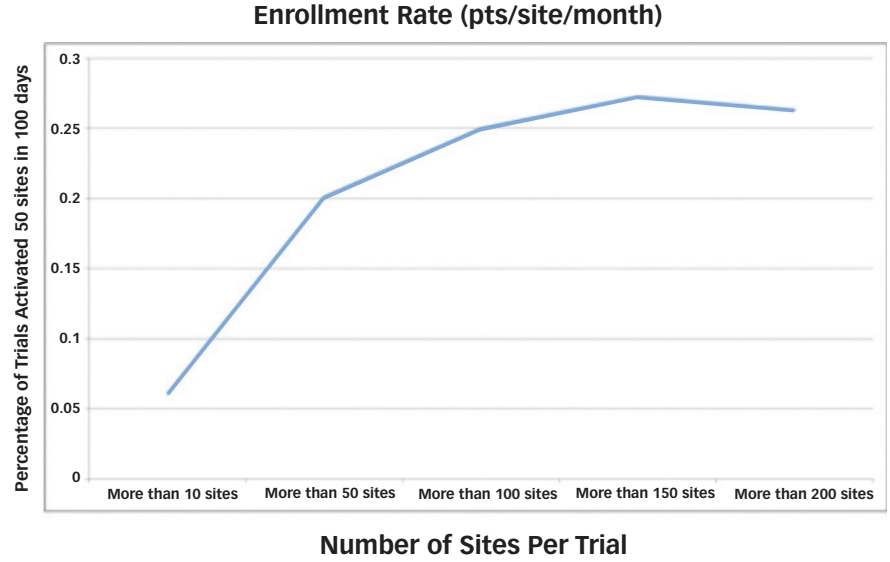
Source: Legagneur et al.

Figure 2. Distribution of site size in the last 10 years.

> We learned from historical sponsor and industry data that it would take an extraordinary effort to activate 50 sites in the first 100 days. From our analysis, it usually took even longer to activate the next 50 sites.

In order to help us to define a more realistic SEI, we examined the site activation curve of a trial with a similar indication from the same sponsor (see Figure 4 on page 36). In this trial, the site activation index was 60%. This is one of the best executed site activations by this sponsor in the same therapeutic area. For an ASER of 0.11 patients per site per month, GSER is 0.067 patients per site per month (0.11x60%=0.067). This led us to recommend that the sponsor should use 120 sites to enroll 292 patients, and we forecast an enrollment cycle time of 36 months (292/(120x0.066), instead of 22 months.

Weighing Performance Goals



Source: Legagneur et al.

Figure 3. Measuring the activation rate as trials grow in scale.

Results

The enrollment was carried out from the beginning of August 2012 to the end of March 2015, a total of 32 months. Figure 5 (see page 36) shows the actual site activation curve.

This chart helps to visualize some of the issues in the implementation of this trial. Thirty percent of sites were activated in the last six months of the enrollment period. For that reason, the enrollment contribution from those 77 sites was very limited, leading to the majority of those sites being nonperforming sites.

While we recommended using 120 sites for the trial, the team actually activated 227 sites instead. However, when we examine the results closely, there were only about 140 sites that contributed patients, much closer to the number of sites that we suggested.

MORE OPPORTUNITIES TO ACCESS THE LATEST INDUSTRY NEWS FOR FREE

Applied Clinical Trials

Ensure that you and your colleagues keep up-to-date with the latest news by subscribing to the following **FREE** e-newsletters from *Applied Clinical Trials*.

ACT DIRECT/WEEKLY

Each edition of ***ACT Direct*** features a premium collection of news, blogs, an advertiser Marketplace, events/webinars, and more. Each edition also features topic specific news, articles and events on a rotating basis. Topics include risk-based monitoring (RBM) and oncology.

ACT TRENDS/TWICE A MONTH

ACT Trends is delivered twice a month to provide the most popular clinical trials news and articles, and highlights what's trending on social media.

SUBSCRIBING TO BOTH TITLES TAKES LESS THAN A MINUTE. **SIMPLY VISIT:**

www.appliedclinicaltrialsonline.com/act-products-subscribe

EFKS/shutterstock.com

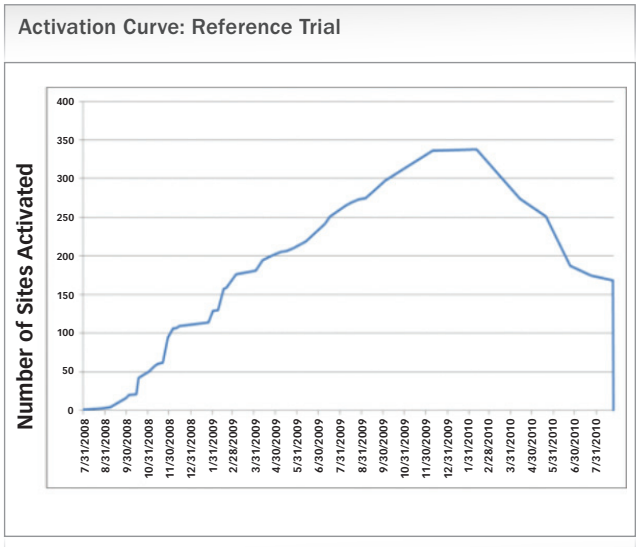
From PhESi internal analysis, it is consistent that the nonperforming sites increase proportionally when more than the optimized number of sites are used.

The SEI for the site activation process was 44%, lower than the 60% SEI value that we recommended.

The forecasted GSER was 0.067 patients per site per month. The actual GSER, calibrating the impact from the 77 sites, was 0.061 patients per site per month.

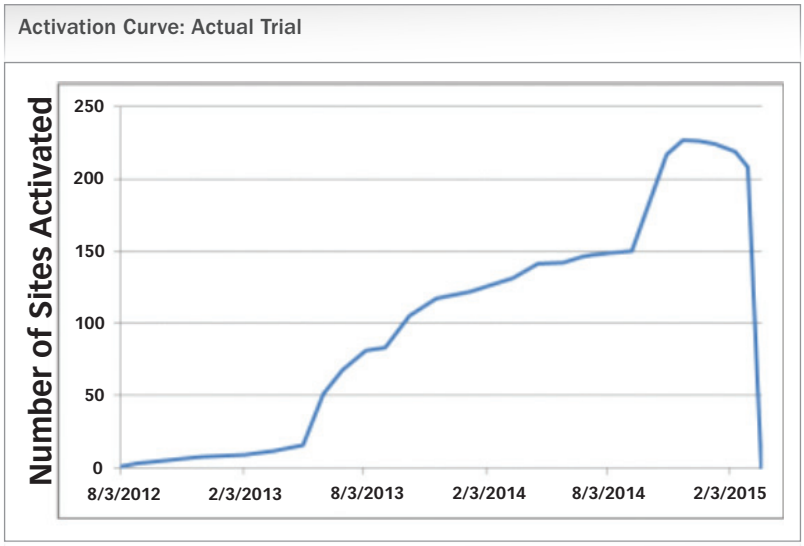
Ironically, we recommended multiple batches of site activation in our plan:

Only activate 70% of the sites in the first batch. This is based on a limited number of experienced sites in clinical trials in this hematology indication and draining energy during a long enrollment period. At six months, we can activate the remaining 30% of PhESi-recommended sites, as they are identified as top enrollers in the next six months (post FSI). This is the choice between 30% of the second-class sites with six months-longer enrollment time, or 30% of top-rated sites with six months-shorter enrollment time.



Source: Legagneur et al.

Figure 4. Site activation in trial with similar indication.



Source: Legagneur et al.

Figure 5. Site activation in the hematology trial.

> Defining site enrollment performance with a metric that is focused on the site enrollment rate suggests that the way to improve recruitment cycle times is by focusing on getting the best possible sites and site-level enrollment enhancement initiatives.

The implementation of a two-batch site activation would have allowed us to more accurately define the number of sites required in the second batch—and when the second batch of sites should be deployed based on the site performance of the first batch of sites. This would maximize the benefit of shortening enrollment cycle time. Taking this approach, it would have been entirely possible to have achieved a 32-month enrollment cycle time by using 120 sites, as we had recommended.

Discussion

Traditionally, we measure patient enrollment by the number of subjects enrolled per site per month, which we call the enrollment rate. This measure implies that patient enrollment is basically a site performance issue. In other words, defining site enrollment performance with a metric that is focused on the site enrollment rate suggests that the way to improve recruitment cycle times is by focusing on getting the best possible sites and site-level enrollment enhancement initiatives. Some sponsors formulate their business processes based on this assumption. Not surprisingly, these organizations often run into costly situations when targeted enrollment timelines are delayed.

In this case study, as in any others that we have worked on, it has been demonstrated that site activation is an important driver in determining enrollment cycle time.[3] There are operational limitations on the number of sites that can be activated in a defined time period, which restricts the total number of patients that can be enrolled.

Another area of limitation is the question of how many sites can and should be deployed in a trial. The dominant thinking in our industry is still misguided on this point. Sponsors believe that if more sites are added to a trial, they will be able to proportionally reduce enrollment cycle time. The obvious fallacies for this thinking is that it implies that if we can add an infinite number of sites to a trial, then we can reduce the enrollment cycle time to near zero!

In our analysis, for clinical trials in any extensively studied disease indications, enrollment cycle time can always be minimized (the "sweet spot") by deploying the adequate number of sites (PhESi internal analysis). See Figure 6.

When we step too far out of the sweet spot, (for example, extrapolating the enrollment rate from a Phase II trial to a Phase III trial in the same development program) we can end up in a rescue situation (PhESi internal analysis). See Figure 7.

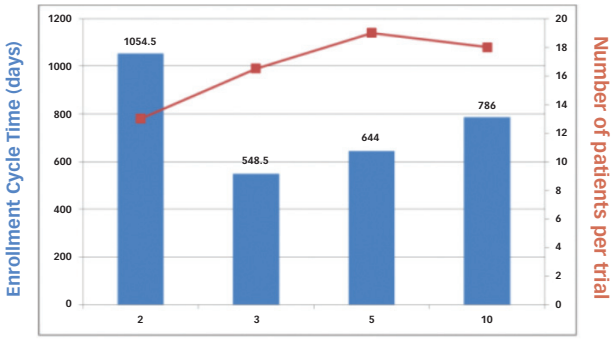
Objective feasibility gained from our analysis in this cancer trial also allowed the sponsor to improve its relationship with its contract research organization (CRO) partner. By incorporating improvement actions recommended by PhESi, the trial completed in the time frame we recommended.

> In planning our trial here, we had to define the optimized number of sites with similar logic, since we could not calculate that "sweet spot" empirically without sufficient historical data.

Fortunately, the problems described in this article were identified in the planning phase, which allowed the sponsor to avoid potential conflict among key stakeholders, and prevented another possible rescue mission from being required.

Retrospectively, our plan was not perfect. We should have explicitly spelled out the nonperforming site issue. If we had incorporated nonperforming sites, we could have recommended to the team to deploy 150 sites, expecting 120 sites to enroll one or more patients. Having learned from this experience, nonperforming site analysis is now a regular component of our analysis.

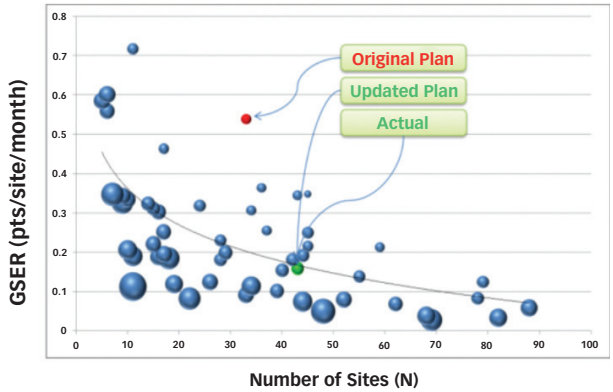
Finding the Balance



Source: Legagneur et al.

Figure 6. The importance of deploying the adequate number of sites.

Risky Models



Source: Legagneur et al.

Figure 7. Venturing from "sweet spot" can result in rescues.

References

1. Gen Li, 2015, Forecast Enrollment Rate in Clinical Trials. *Applied Clinical Trials*, Volume 35, Issue 3, pg 42-48
2. Gen Li, 2009. Finding the Sweet Spot. *Pharm Exec*. Published October 2, 2009. Available at: http://www.pharmexec.com/finding-sweet-spot?id=&pageID=1&sk=&date=
3. Gen Li, 2008. Site Activation: The Key to More Efficient Clinical Trials. Pharm Exec. Published December 12, 2008. Available at: http://www.pharmexec.com/site-activation-key-more-efficient-clinical-trialsGen Li, 2009. SITE EFFECTIVENESS INDEX AND METHODS TO MEASURE AND IMPROVE OPERATIONAL EFFECTIVENESS IN CLINICAL TRIAL EXECUTION. U.S. patent publication No. 2010-0250273
4. Gen Li, 2014, METHODS OF FORECASTING ENROLLMENT RATE IN CLINICAL TRIALS, U.S. Serial No. 14/818,438, filed August 5, 2015, which claims the benefit of U.S. Serial No. 62/033,844

Valerie Legagneur *is Vice President, Clinical Operations, Odonate Therapeutics, LLC;* ***Jonathan Peachey*** *is Head of Client Services, PhESi, LLC;* ***Karen Correa****, PhD, is Senior Director, Clinical Operations, Adare Pharmaceuticals, Inc.;* ***Gen Li****, PhD, is Founder and CEO, PhESi, email: gen.li@phesi.com*

** Acknowledgement: Valerie Legagneur and Karen Correa were formerly employees of Pfizer, Inc. Adrian Li provided editing support.*

Any Cancer Can Be a 'Rare Cancer'

Cancer "rareness" means more than cancer incidence. It's about the molecular makeup of each tumor.

Stephen Gately, PhD
is President and CEO of TD2

In the earliest days of science, researchers thought that if you had cancer, you just had cancer. Then, as classifications evolved, they thought if you had lung cancer, you just had lung cancer. But now, advanced molecular profiling has necessitated a more complex analysis: You not only have lung cancer, you have EGFR mutated, KRAS mutated, or ALK gene rearrangement non-small cell lung cancer.

Welcome to the driving force behind the precision medicine movement. We've taken a general disease, narrowed that down to a specific disease classified by its organ of origin, and further classified the cancer by one or more defining genomic defects.

The process has turned the term "rare cancers" on its head. You might not consider lung cancer, which is diagnosed in 234,030 patients a year, a rare cancer. But what about ALK+ non-small cell lung cancer, which is diagnosed in just under 10,000 patients every year?

Because those 10,000 patients have a specific type of lung cancer, they don't respond to the standard treatments that work for most people. Instead, they need drugs made specifically for their genomically defined cancer.

The same thing goes for those who have other cancers few people have heard of, like small intestine cancer, which also affects about 10,000 people a year. Small intestine cancer is a "rare cancer," but so are certain types of more commonly diagnosed cancers—because cancer "rareness" means more than cancer incidence. It's about the molecular makeup of each tumor.

That's why the future of research for any cancer is entirely, and unequivocally, molecular. Drugmakers have caught on—and it has changed the calculus for cancer research.

Investigators should no longer pack as many patients as possible into a global clinical trial just to find responses to a new medicine in a few patients. Instead, they need to identify patients whose cancers share molecular defects, and match those molecular defects with a medicine that targets that particular defect.

You might think that finding very specific people with very specific diseases slows down research. And in a way, it can…at the start.

But here's the reality: Targeted clinical trials yield the most dramatic results. When tumors rely on a single genetic mutation, medicines that target those mutations see response rates as high as 100%.

And if you're a drugmaker, clinical investigator, or patient, once a new medicine makes headlines touting its benefit in nine of 10 patients, any slowdown is quickly reversed. People get excited and there is a singular focus on getting the medicine approved quickly by the FDA.

Then, it's not about finding the right patients—the right patients find the right medicines.

That's what happened with Gleevec, the milestone drug that marked the first step in molecular profiling. Built for patients with chronic myeloid leukemia (a rare subset that affects about 10% of leukemia patients), Gleevec saw an 88% response immediately. These were the patients for whom other drugs had failed.

In many of these cases, you don't need a lot of patients to respond in order to get a drug approved. They're rare cancers, after all. This kind of drug discovery means that researchers can spend less time in development, get their drugs approved faster, and start helping patients immediately. It just requires a sound clinical strategy that targets the right people.

When I think of the impact that one small change could make on the lives of patients, it gives me hope. I think of patients with uveal melanoma, which has zero drugs approved for treatment. I think of patients with fibrolamellar hepatocellular carcinoma that impacts young adults and has no drugs approved for treatment.

Each is a rare cancer in its own right. Each has known molecular or genetic defects. We need to find the right drugs to match to these cancers. Precision medicine provides physicians with the opportunity to avoid less effective treatments and focus on rationally selected medicines that improve clinical outcomes for patients.

wcg clinical services™

Designed to make every second of your enrollment period count.

Achieve enrollment timelines with a customized, end-to-end recruitment plan from WCG Patient Engagement services. Backed by proven methods, a knowledge base of industry site enrollment performance, and our on-the-ground site support, we partner with you to enable your sites to achieve recruitment milestones on or ahead of schedule.

These efficiencies could amount to you saving two months in patient screening time, or 4,838,400 seconds. **Make the most of every second.**

www.wcgclinical.com/patient-engagement

Improving Pharma R&D Efficiency

Pharma business models are under significant pressures to improve R&D efficiency and deliver cost savings.

A new survey of pharmaceutical executives and professionals by ICON and Pharma Intelligence provides valuable insight into key clinical trial challenges and potential solutions.

We explore the areas identified by industry experts as having the most potential for generating savings and improving trial efficiency, and how digital disruption is forcing change.

Download whitepaper

ICONplc.com/pharma