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APPLIED CLINICAL TRIALS

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Next-Generation Clinical Trials

LISA HENDERSON
Editor-in-Chief

Going into the planning for our September issue, we called this the "Status of Clinical Trials" issue. But what we really wanted to look at was the status of next-generation trials. The strategies that industry is currently taking to address the limitations in clinical trials such as lack of efficiencies or poor patient participation. Or technologies or business models that have advanced to again address the well-noted challenges in clinical trials.

To support that mission, we've included articles from the start to the end of the clinical trials process. From using modeling and simulation in drug discovery or protocol design; to conducting drug tests not in humans, but on their cells in a dish to determine efficacy; to the advances of genetic testing that will advance research and personalized medicine and patient considerations in regard to that testing. Of course, technology has a huge role, so we explore continued use of mHealth, as well as technology uses to improve finding the right patients for the right trials.

A significant part of the patient recruitment problem continues to be education—the knowledge that everyday people have about clinical trials; location—the ability to take part in a clinical trial that is not burdensome; and trust—the ability to put your health in another person's hands, when you usually deal with one healthcare provider. And in these areas, too, are advances in technology and business approaches.

Our first Q&A (see page 8) features an interview with the executive director of Greater Gift, which offered a chance for clinical research teams to meaningfully inform the public about clinical trials in a variety of venues. In the quest to bring clinical trials closer to patients, we profiled new business models that change the site landscape, including impacts on virtual trials, specialty practice physician groups, large integrated delivery health networks, and dedicated sites (see page 15). And, of course, the underlying advances for all the new models feature an aspect of technology, be they EHR integration or a network or platform to interface with patients, or technology that matches patient biomarkers and genetic information to the right clinical trial.

Reading the articles separately, the reader will hopefully come away with an appreciation for the changes that individuals and companies are bringing to improve the clinical trials process. But taken as an aggregate, you will hopefully see a moving needle, where not just one thing is going to revolutionize and improve clinical trials. Rather, you will see the promise that advancing technology and science brings to medicine—and glimpse the promise of the future.

Currently, in order to improve health or quality of life, people travel miles across countries to receive the right treatments and the right care. One of the most engaging phrases to come out of this next generation of clinical trials is its "democratization" or the action that makes something accessible to everyone. The option for a person to participate in their own health and influence their own genetic path is a reality. The option for a person to choose a clinical trial as a care option, right there at the point of diagnosis, is coming closer to reality. The option to advance science in a more personal and meaningful way, that will be the democratization of clinical trials.

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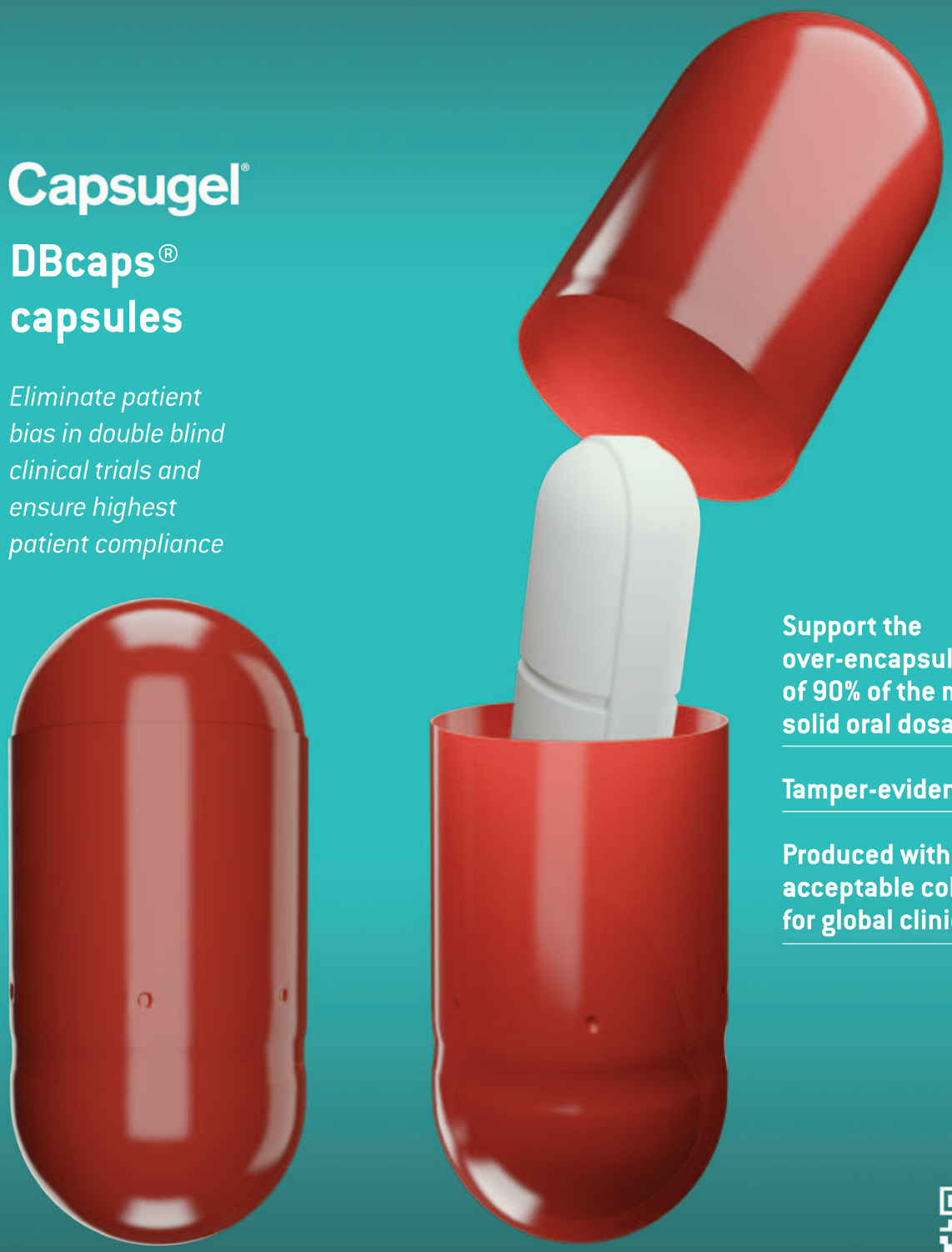

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WASHINGTON REPORT

FDA PROMOTES SURROGATE ENDPOINTS, 'SEAMLESS' CLINICAL TRIALS

As part of efforts to speed patient access to effective new therapies, FDA is rolling out policies designed to streamline drug development, particularly for new cancer therapies to treat life-threatening conditions. A new guidance outlines how sponsors may compress the traditional three-phase trial into one continuous, or "multiple expansion cohort study," to reduce the time and cost involved in devising trials for early stages of multi-phase oncology research programs.

The draft guidance maps out the process for shifting from the traditional clinical trial process to a continuous, or adaptive, study to expedite the conduct of first-in-human studies for patient populations with serious diseases where no cure is available (see http://bit.ly/2nZ0vN7). This approach utilizes a single protocol with an initial dose-escalation phase to determine a potentially effective dose. That dose then can be evaluated for safety and effectiveness in additional patient cohorts, similar to the role of Phase II studies. FDA recognizes that such trails may expose patients to drugs with unknown toxicity and possibly limited benefit, and thus limits this approach to studies involving individuals with serious conditions. The agency also requires sponsors to establish systems for rapid data collection and evaluation and for continual oversight to quickly detect unexpected results.

FDA also is encouraging wider use of surrogate endpoints in clinical research by publishing a list of those markers that sponsors have used to gain approval of new drugs and biologics. The list was specified by the 21st Century Cures Act to facilitate medical product development. It provides information on surrogate endpoints that have supported market applications, as well as those utilized as primary endpoints in trials, but not as the basis for filing a new drug application (NDA) or biologics license application (BLA) (see http://bit.ly/2Cp9HEB). FDA notes that it will evaluate the use of surrogate endpoints in a particular development program on a case-by-case basis, and that it will update the list every six months.

FDA Commissioner Scott Gottlieb heralded the seamless trial approach as a way to avoid costly and long delays between the end and start of clinical study phases (see http://bit.ly/2nZ0vN7). FDA outlines in the guidance which drugs are best suited for expansion cohort studies, what information sponsors should provide in investigational new drug (IND) applications to support such studies, safeguards needed to protect patients, and when to consult FDA on planning and conducting these types of innovative studies. A main theme promoted by Gottlieb is that more efficient research approaches can lower the cost of drug development and translate into less expensive new therapies, but such benefits have not been that apparent.

Senate spending bills give minor boost to agency

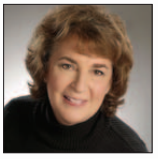
Instead of taking the usual August recess, the Senate stayed in Washington to approve several multi-agency budget bills for the government fiscal year that begins Oct. 1. The measures boost funding for FDA and the National Institutes of Health (NIH)—and include a contentious provision that requires biopharma companies to disclose product prices in direct-to consumer (DTC) advertising.

The DTC ad measure was added to a major Senate appropriations bill for the Departments of Labor, Education and Health and Human Services (HHS). That legislation provides a $2.3 billion increase in NIH funding, to $39 billion, with some of that directed to combat the opioid epidemic by supporting NIH research to develop non-addictive pain therapies.

Most notable is an amendment that aims to provide consumers with more information on drug costs by instructing HHS to develop and implement rules requiring manufacturers to list drug prices in ads. This provision most likely will involve a formal rulemaking process to clarify what information (list or discounted prices?) should be disclosed and how the policy would be implemented.

In another major funding bill for the Department of Agriculture and other agencies, the Senate approved a $159 million budget increase for FDA, to bring its resources up to $5.4 billion for 2019, including more than $2 billion in user fees. The Senate plan, though, provides much less than the $400 million hike for FDA requested by the administration, and is well below the $308 million boost approved by House committees. The Senate provides FDA an additional $88.5 million to enhance medical product development and oversight, compared to $260 million proposed in the House, with the added funds directed to advance drug and medical device manufacturing, modernize general drug development, and support new science to evaluate drugs.

Senate leaders hope that their House colleagues will agree to negotiate final funding packages through conference committees, instead of waiting for formal House approval of separate budget bills. All parties want to finalize these spending bills before Oct. 1, when the government could shut down without approved funding for the 2019 fiscal year.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

9/5/18: Allergic Rhinitis: Developing Drug Products

8/10/18: Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics (draft)

7/23/18: Inborn Errors of Metabolism that Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development

7/18/18: Use of Electronic Health Record Data in Clinical Investigations

7/17/18: Innovative Approaches for Nonprescription Drug Products

EU REPORT

CAN FDA PUT SOME HEAT BACK UNDER EUROPEAN ADAPTIVE PATHWAYS?

The FDA's August release of draft guidance on innovative clinical trial designs for cancer therapies has excited interest not only among the US oncology community but also among some far-sighted drug developers in Europe, too. The FDA document, "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics" (http://bit.ly/2nZ0vN7), offers advice on designing and conducting adaptive designs that can assess multiple aspects of a drug in development in a single trial while enrolling the minimum number of study participants.

The essence of these first-in-human multiple expansion cohort trials is that they can expedite development by proceeding seamlessly from initial determination of a potentially effective dose to individual cohorts, with trial objectives more typical of Phase II than Phase I trials. An FDA statement accompanying the release stresses the merits of targeted treatments, and records rising patient demand to enter these early trials and increasing calls to speed development and approval processes. The advantage of addressing multiple questions in a single trial that is amended as new objectives are identified is to avoid the time lag and additional resources experienced with the opening of new clinical trials, says the FDA.

The avowed objective of greater efficiency in drug development that can make highly effective drugs widely and rapidly available to the public could play well among drug developers in Europe. So, too, will the tone of the FDA invitation to comment: "We want your input to make sure that the final guidance is comprehensive and forward looking and adapts to rapidly changing research developments and technologies. Our regulatory work needs to remain as advanced as the many new cancer therapies currently working their way through development."

The drive in Europe toward adaptive pathways today gives every appearance of having run into the sand. Half-forgotten now are the heady days earlier in this second decade of the 21st century, when the European Medicines Agency (EMA) ran a pilot project to explore accelerating market access for new medicines.

Around 2015, the potential downsides of targeted medicine and adaptive pathways started to dominate European debate. Prominent European scientists raised concerns over the EMA pilot, questioning the conflation of "new" and "innovative" or the assumption that early market entry is beneficial to society, and flatly rejecting the principle that, "something is better than nothing." The European Public Health Alliance attacked the EU approach on the grounds that it had "prevented and impeded any political scrutiny." The European consumer defense body, BEUC, got in on the act with a study whose focus was clear from the title: "Fast-track approval for new medicines – patient safety at risk?", and which warned of the "unnecessary health risks" of adaptive pathways "because these medicines would be put on the market before there is complete information about their safety."

Even more substantially, the highly influential German health technology assessment body known as IQWiG (its name in English means the institute for quality and efficiency in healthcare) judged the EMA-backed approach as leaving "open questions unanswered"—particularly what it termed "perplexity" over the concept of real-world data. IQWiG said it "again sees its concerns about adaptive pathways confirmed," because "evidently neither industry nor EMA has a concept as to how real-world data can be used after drug approval to allow drawing reliable conclusions on benefit and harm." Since real-world data is "a key component of the adaptive pathways concept," uncertainty over its nature, its availability, or access to it means that the whole concept needs rethinking, said IQWiG.

Battered by such allegations, the topic has slipped down Europe's strategic agenda. The FDA draft guidance may restore some vigor to the debate. With its careful enumeration of recommended safeguards, the U.S. document not only makes some contribution to detailing protective mechanisms on the specific questions surrounding expansion cohorts, it also brings a balanced approach to the broader issues of adaptive pathways as a concept. Alongside its forward-looking enthusiasm, it sets out cautions over patient safety and methodological integrity in what amounts to a thoughtful outline of the pros and cons.

"It is critical that investigators, institutional review boards (IRBs), and regulators are updated with new safety information so that they can provide the necessary oversight for protection of human subjects and so that investigators can ensure that patients can provide adequate informed consent," it continues. And it warns against "inefficient drug development based on possibly missed interpretation of preliminary trial results and unplanned analyses that can lead to delays in proper clinical development."

The guidance also urges tight constraints on patient populations. Informed consent documents should be updated as new information is obtained during the trial that may affect a patient's decision to participate in or remain in the trial. Ethics review boards should frequently review evolving new safety information, and the background information for each expansion cohort should contain the scientific rationale for that individual cohort, with descriptions of the prespecified stopping rules.

The relative inactivity of European regulators on adaptive pathways is in part down to Brexit. The distractions for EMA of having to move from London to Amsterdam by next March has severely impacted its ability to do anything more than keep up with its core activity of assessing and monitoring marketing authorization applications. Adaptive pathways is simply one more extra task on which EMA and the Commission were due to act two years ago, but which has been neglected for pressure of resources, admitted the EU health commissioner in mid-August.

However, Europe hasn't completely gone into hibernation on the subject. Since 2015, an EU-backed project, ADAPT SMART, has been working quietly away at—in its own words—"laying the foundations and building consensus to make adaptive pathways work for all." The latest FDA entrance into the debate may help.

— Peter O'Donnell

Q&A

CLINICAL TRIALS NEED TO GROW IN RELEVANCE

Non-profit organization Greater Gift provides a vaccine to a person in need for each person involved in a clinical trial with one of its partner organizations in an effort to celebrate clinical trial participants and raise awareness for study participation. Ahead, the group's executive director, Amanda Wright, discusses its program and the state of clinical research. Wright began her career as a clinical research coordinator and moved on to serve in various leadership roles in operations, patient engagement, business development, and marketing.

Q: You have a long history in clinical research. How did you become the executive director of Greater Gift?

WRIGHT: I was very fortunate in that I was involved in Greater Gift since the day it was conceptualized. And when the former executive director decided to transition to a new role and a new opportunity, it seemed to be the right time, the perfect fit for my interests, and really a direct complement to the work that I was doing at the time, specifically within patient engagement.

Patient engagement was something that very early on in my career peaked my interest. In a clinical role more than 20 years ago, it was a core element of what I was doing as a clinical research coordinator; so it seemed to come together at the right time and it's certainly something that I've enjoyed and has been a passion of mine since the very beginning and continues to be.

Q: Greater Gift's most recent PopUp Star Event was very successful (see http://bit.ly/2wq3BO8). Can you tell us more about that and your plans for moving the event and its initiatives forward?

WRIGHT: The event was a great success; and like anything you do the first time, there was a learning curve, with some days steeper than others. When you consider the results of the competition, which ran for 10 days, and at the end of those 10 days we were able to engage over 1,500 people in a conversation around clinical research, you can only be proud. When you think about the magnitude of that and consider the likelihood of this occurring without the event, you have to step back and say that's a success. And not just for those 1,500 people that we were able to talk to about clinical research, but also the networks of those people, and how it impacted those people who were engaged as event organizers; it's powerful and I'm very proud of it.

We are currently evaluating what we learned and pulling together strategic minds and organizations to determine what the next iteration may look like. I'm confident in saying we will put all the feedback and insights to good use and bring forth another meaningful event.

Q: You have lived in the Winston-Salem, NC, area for over 40 years and are plugged into companies advancing health and research there. What is going on in that area that makes it special for clinical research?

WRIGHT: There's a deep foundation for what's happening now in Winston-Salem. We are fortunate in that we are in a city where we have two major, top-tier health systems—one being an academic medical center—that serve as anchors within the community. In addition, our city is, and has been, transforming through major revitalization and economic development plans for the past 15 years. Efforts have been centered on innovation and diversifying community collaboration and engagement for the success of the city and to the benefit of our community and beyond, and I think that in itself creates an advantage for clinical research professionals and clinical research interests. There are a number of parallels between what is happening in our city to revitalize our community to the clinical trial process.

Our city has a history of success through unique collaborations and prioritizes initiatives designed to improve the lives of the people within our community. I think that's why clinical research fits perfectly. When you have a profound history as we do in medicine, along with a culture of innovation, really there is no better place for clinical research. We are also fortunate that our local government and community leaders have been encouraging of the clinical research enterprise within our city. I think that's a tremendous driver.

Q: What single-most change in clinical trials do you think could bring the most positive impact to the enterprise?

Amanda Wright

WRIGHT: This may not be the typical response, but the greatest impact would be for clinical research value to be recognized across a wide variety of stakeholders, including not just healthcare, but groups like payers, government, and the broader community. That will have tremendous impact on how we collectively come together to advance public perceptions of clinical research and ultimately increase engagement in clinical trials. Such recognition of value could significantly impact many of the challenges that we face, from how long it takes to get a drug to market to the cost of getting a drug to market and in the hands of those in need. When effectively structured, clinical research could be an effective countermeasure to cost, care, and outcomes, or what we know today to be population health. Yet, we continue to have extremely low participation in trials. I believe with the appropriate value recognition, clinical research will experience increased participation, which leads to a shift in both time and cost; clinical research becomes relevant.

While there are many interventions that could improve the clinical research enterprise, and there are certainly a number of technology solutions that would fit the bill, without the relevance, we cannot do the best job developing those technologies, nor will they be adopted at rates that translate to high impact. By making clinical research relevant, the other pieces will fall into place and we will make better decisions around those solutions to support the clinical research enterprise, instead of expecting these interventions to drive the enterprise. Relevance has to drive it.

—Staff Report

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Q&A

PACT FOCUSES ON EXPANDING CLINICAL RESEARCH ACCESS

Syneos Health and Elligo Health Research recently initiated a partnership on a system of accelerated research (SOAR). Here, Michael Gibertini, chief clinical innovation officer, and Clare Grace, VP of site and patient access, both with Syneos Health, and John Potthoff, CEO of Elligo Health Research, explain what the plan will entail.

Michael Gibertini

Clare Grace

John Potthoff

Q: Can you talk about the goals of SOAR and what clinical research as a care option means to you?

GRACE: Traditionally, we have asked patients to travel to research sites to participate in clinical trials, placing a heavy burden on the patient. By embedding clinical research into the care setting, we are able to bring the research directly to patients at their physician's office. There's a huge benefit to integrating research into the care continuum because patients are in their sphere of comfort, familiarity, and trust.

This SOAR approach also supports physicians and the care infrastructure. Not only does it support the cost of delivering that care, but it also enables physicians to be at the forefront of research and medicine. That's attractive to many healthcare practitioners and physicians.

GIBERTINI: Syneos and Elligo are in the early stages of our collaboration, which will span developing the SOAR system and testing the model with a study. It will include support from a clinical research and regulatory standpoint, allowing for a centralized research effort. By reaching out to community physicians and engaging them around their patients, we will bring patients who don't typically participate in research into a research project.

POTTHOFF: All patients should have the option to participate in a clinical trial matching their healthcare needs while under the care of their own, trusted physician. Elligo provides infrastructure, technology, and expertise to physicians, which helps provide patients access to trials. SOAR is a further extension of this model that facilitates reach to more physicians and patients. In this model, we do not activate study sites—we activate a central system of research that controls the research process for each patient through their local physician.

Q: How does SOAR contribute to these initiatives?

GIBERTINI: SOAR will allow patients with serious and complex diseases to participate in research in the comfort of their own physicians' office, with access to specialty care and the assessments that go into clinical research. The advantage is, they won't have to go anywhere else. SOAR enables specialized treatment, supporting physicians and the system to deliver that care.

POTTHOFF: The new system of research democratizes participation by removing both the administrative burdens and the physical barriers that impede patient and physician participation. We seek to keep the trusted patient-physician relationship intact while allowing participation by patients from virtually anywhere in the country.

Q: What are the key benefits of SOAR to stakeholders?

GIBERTINI: Bringing clinical research to underrepresented populations through community medical practices—evolving from a location-bound approach to a centrally managed approach—redefines the clinical trial site footprint. Our partnership will leverage electronic heath record access and systems to drive new research concepts and innovation, benefiting patients who don't typically participate by providing more access to cutting-edge care. This effort should improve quality, reduce timelines, and save costs.

POTTHOFF: Patients participating in a clinical trial often receive a more thorough evaluation of their health needs and more time with their healthcare providers than those who don't participate.

Physicians have more resources to evaluate their patients and better access to information. When clinical research is integrated into the healthcare environment, patients have the ability to make a treatment decision from options that include both standard clinical care and clinical research. Furthermore, the model will improve patient retention and protocol compliance, thereby driving advances in clinical research.

Q: How are you reaching patients to make research as a care option viable?

POTTHOFF: Patients in real-world healthcare often have more complete histories and medical records than patients recruited into a clinical trial previously unknown to the physician. And you can't get more real-world than actual healthcare practices. Using healthcare data, we can detect patients who match study criteria at a particular physician practice, all in a de-identified, HIPAA-compliant way.

Physicians are fully capable and interested in the medicine of a clinical trial. Under the framework of a central research system, there is no administrative burden or added cost for the physician to offer clinical research to a patient. As an industry, we also need to make it easier to learn about available trials and be responsive to patients and physicians who may be seeking information.

Q: Industrywide, what are the biggest challenges to fully integrating clinical research as a care option?

GRACE: It really depends on the trial, the patient, the geography, and a multitude of other considerations. Awareness is one. Many physicians and healthcare practitioners aren't as aware of current research, what research is about, and how to conduct it effectively.

There's also the operational challenge of integrating into a site that has no research experience. There are different monitoring

Q&A

requirements, needs, and oversight for sites that don't have SOPs.

For example, if you have a rare disease or oncology trial, the patient/physician relationship is very intense over a long period of time, and it is quite contained. It's a very specific relationship. Whereas if you're looking at research in primary care, the relationship is more fluid and transactional. You must take that into account when you recruit patients and physicians to participate; in most cases, they're research-naïve, so support is required to ensure the site operates effectively.

POTTHOFF: I think the biggest challenge is geographic adversity: physicians treating smaller numbers of patients are not selected as clinical trial sites due to low expected enrollment compared to the cost of activating that site. Central research systems utilizing advanced technology and telehealth remove this barrier. It is our goal to make it easier for patients to participate in clinical research.

— Staff Report

DRUG ACCESS

THE EUROPEAN DRUG PRICING DILEMMA LURCHES FORWARD

The summer did see one very positive development in the faltering attempts by Europe's governments to resolve that challenge of providing patients with innovative medicines without bankrupting health budgets. In July, a joint decision on reimbursement was reached by two European countries on an expensive new drug—very much a first for a continent divided by dozens of distinct national pricing authorities.

Belgium and the Netherlands reached an agreement with Biogen on the pricing and reimbursement of Spinraza, the company's nusinuren, indicated for 5q spinal muscular atrophy at a list price of close to $1 million per patient. After three years of cooperative efforts aimed at conducting joint negotiations with drug companies, they have at last got a result. Negotiations began in February, and involved a joint health technology assessment as well as three-way talks between Biogen and the Belgian and Dutch health ministries. Spinraza will be reimbursed for specific groups of patients in both countries under similar conditions, and at a price that both countries characterized as "acceptable"—although neither revealed just what the agreed price was.

Belgian health minister Maggie de Block was quick to hail the achievement as a watershed moment for Europe—"a giant step forward." So, too, was her Dutch counterpart, Bruno Bruins. He saw the outcome as "a very clear and promising example of the benefits of working together on price negotiations and pharmaceutical policy. "

The success is well-timed, because the Belgian-Dutch cooperation has only recently been expanded to five countries, and this makes it look as though the so-called Beneluxa exercise is more than just a talking shop, or a vehicle for smaller countries to vent their resentment at being picked off one by one and victimized by the big battalions of international pharma in pricing talks on innovative medicines.

It is also well-timed since something like a tipping point has been reached in the entire discussion of how far European countries can find common ground in their dealings with big pharma. One of the other leading attempts to work together—known as the Valletta process—appears to be in serious trouble as it tries to define the next steps toward its avowed goal of achieving "fair" prices for new medicines. Greek Health Minister Andreas Xanthos outlined the challenges as he hosted a meeting of the group in Athens in mid-July, and he frankly admitted that despite the readiness of the 10 signatory countries from southern and eastern Europe to go beyond exchanging information and expertise, the drug industry is not going to play ball unless there is more clarity about its legal status and its procedures. "We share the political will to work together and we have some strong common views," he said. But, he went on, the diversity of national laws is holding back progress, and "reinforcing the expected reticence of the pharmaceutical industry."

"Reticence" among research-based drug firms has been evident, out of apprehension that premature commitment to such embryonic systems could divert previous management resources, increase rather than decrease the tasks involved in pricing negotiations, and even damage their own ability to maintain the revenue cycle that funds their research. Vertex negotiated at length and at a high level with Beneluxa before eventually both sides pulled out of talks because it was impossible to agree on a mutually acceptable price. Others have backed off sooner, discouraged by the risk of additional bureaucracy. The disparate membership of the Valletta group, mixing countries of different sizes and wealth, makes engagement even more of a challenge than with the more homogeneous Beneluxa group. So, too, does the Valletta approach, spelled out by Xanthos: "The pharmaceutical industry joins forces to exert greater influence on political decisions. It is time for us to do the same thing."

Xanthos recommended that the Valletta group should set up a new regulatory framework that could offer drug firms rapid access to a market of its 160 million citizens. He also called for more regular well-prepared technical meetings to move toward an international convention to bind national health systems, patients, and the pharmaceutical industry. An ambitious approach. But first it will be necessary to get the drug industry back to the Valletta negotiating table—and since the last joint discussion between industry and health ministry sherpas broke up in some disarray last March, there has been no further contact, and as summer set in across Europe, no date on the horizon for a resumption.

— Peter O'Donnell

CLINICAL TRIAL INSIGHTS

PLACING A PREMIUM ON INFORMED UPFRONT PLANNING

Reexamining traditional cycle-time reduction strategies is critical for sponsors, CROs, and sites

Ken Getz

Sponsors and service providers share the blame equally for creating an industry-wide obsession with reducing cycle time. Indeed, for as long as I can remember (going back nearly 30 years), the typical value proposition during a sales call has focused on the promise of a new product or service reducing delays and accelerating development cycle time to drive huge revenue gain in additional prescriptions written. Many vendors have priced their product or service accordingly, basing its value on the opportunity cost of a longer period of patent-protected pharmaceutical sales.

As an enterprise, we drill our obsession with shortening cycle times into all aspects of drug development planning and execution. A simple concept has ruled the day: "Time saved equals more dollars (e.g., revenue) earned." With few exceptions, drug development professionals can recite readily the cost of a single day of delay—now approximately $1.3 million in lost prescription sales—to bring an average performing drug to market.

Quest for speed

Our obsession with speed has invited numerous entrepreneurs and new ventures and has produced a wide range of new and promising services and solutions over the years. Very few, however, have consistently and sustainably produced the desired outcome.

During the past two decades, significant attention and resources, for example, have focused on shortening study start-up timelines to accelerate patient enrollment. The globalization of clinical trials has promised sponsors and CROs access to well-trained investigators and large numbers of treatment-naïve patients. Site identification services, some leveraging commercial and proprietary site selection and patient identification databases, have been deployed. Grant and contract negotiation services and applications have been used with the hope of shortening clinical trial budget and contract approval processes. Performance incentives have been offered to facilitate not only faster start-up but also more rapid enrollment of evaluable patients.

Data management technologies—most notably electronic data capture (EDC) systems—have promised shorter cycle times to capture and clean clinical research data and close out clinical trials. Trial management systems, document routing, electronic trial master files, file sharing, and clinical trial supply management systems have promised faster study conduct by enabling sponsors and CROs to more efficiently monitor project and site performance, deliver study materials, access and share documents, mitigate issue escalation, and review and approve plans and ongoing activities.

Time not saved

Taken together, the many time-saving solutions and practices implemented should reasonably be delivering an investigational drug at 40%—to even one-third—of the historically long average cycle time that it took to develop a drug in the 1980s and 1990s. Yet the industry-wide obsession with shortening cycle times has not delivered its desired intent.

Research by the Tufts Center for the Study of Drug Development (Tufts CSDD) shows that the average development cycle time for the typical investigational drug approved between 2014 and 2017 was 6.8 years—seven months (10%) longer than the average observed 10 years earlier. And Tufts CSDD research has found cycle time increases during the past decade not only at the macro level but also at most functional levels. Total clinical site initiation cycle times, for example—from site identification through first patient in—took 29.1 weeks on average in 2017, up 14% from an average of 25.6 weeks in 2007. And the time from last patient last visit (LPLV) to database lock was an average of 36.1 days in 2017, up 8% from 33.4 days in 2007.

Clinical research professionals and industry analysts are quick to note that the failure to sustainably reduce cycle time is due to a number of factors, including increasingly demanding and complex protocol designs; regulatory compliance burden; the difficulties associated with managing and conducting ever-larger global studies targeting more narrowly defined patient populations; uncertainties associated with staff restructurings, downsizings, mergers and acquisitions, and in-licensing; and the frequent new development strategies, practices, and solutions that companies always appear to be implementing.

Another root cause that is rarely noted, however, is associated with sponsor and service provider failure to adequately plan prior to execution. Indeed, a growing body of evidence suggests that the practices supporting the adage "Time SAVED equals more dollars earned" result in unintended inefficiencies, amendments, change orders, and other delays.

Instead, sponsors, CROs, and investigative sites need to embrace an alternate mantra: "Time SPENT equals more dollars earned."

The value of upfront planning

Cycle-time reduction strategies have primarily looked at compressing the time to perform sequential tasks and activities. Clinical teams and their CROs and investigative sites have raced to move from time A to time B. But few organizations have fully considered the substantial downstream cost of rushed planning and hasty execution.

Consider the following: A 2016 Tufts CSDD study found that the majority of protocols (about 60%) require at least one substantial amendment—each taking, on average, three months to implement at a direct cost of approximately $535,000 per Phase III protocol and $150,000 per Phase II protocol. Phase II and III protocols had a mean number of 2.1 and 2.3 global amendments, respectively. Half of all substantial amendments were deemed "avoidable" by study sponsors and nearly one-third of amendments occurred before the first study volunteer had received the first dose. These results strongly point to the need for, and value of, better upfront protocol planning, review, and feasibility assessment.

CLINICAL TRIAL INSIGHTS

The race to get protocols into the hands of investigative sites has also introduced other unexpected costs. Study staff report that protocols initially reviewed by sites during the request-for-proposal process are often altered after the investigator meeting, thereby rendering some of the protocol review and training insufficient.

In May, Tufts CSDD's in-depth interviews with 45 data management executives found that one of the primary causes of database build and database lock delays was due to clinical teams failing to finalize protocol design decisions in a timely manner. Clinical operations teams were also unable to adequately coordinate the growing number of external data source providers and to set study conduct expectations upfront.

> The rush to do things faster is resulting in longer cycle times as clinical teams and their partners overlook critical steps and revise and redo work.

As another example in the scramble to engage a large number of globally dispersed sites, sponsors and CROs have historically focused on expected enrollment rates only to hit a wall when setting up and coordinating infrastructure in remote regions. One of the largest global CROs reported that on a recent pivotal trial it took three times longer to establish infrastructure and work with health authorities and regulatory agencies in remote regions. A clinical supply manager noted in a recent trade journal article that study drug shipping times to remote regions took twice as long.

These are but a few examples. Individuals close to specific activities and tasks can point to many more cases where the rush to do things faster is resulting in longer cycle times as clinical teams and their partners overlook critical steps and revise and redo work.

Changing concepts and habits

The goal to sustainably reduce cycle time requires rethinking the classic "Time is Money" concept and combining both time-saving and time-spending measures to support and nurture performance success. Performance metrics collected by management and clinical teams need not only measure traditional cycle time but also efficiency, downstream delays, the incidence of remedial practices, and quality. The collection and application of relevant and robust scientific and operating data using more sophisticated and predictive analytics may help inform better planning and decision-making.

There is not only a necessity for time-saving technologies and practices but also a necessity for investing more time upfront into specific tasks and activities to properly engage teams, plan for contingencies, pre-qualify service providers and partners, coordinate various parties, and determine whether protocols are feasible and executable, and budgets and timelines realistic. Doing so will ultimately deliver real and long-term cycle time reduction while improving quality, cost, and efficiency.

— 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

FDA SUPPORTS MORE FOCUSED DEVELOPMENT OF TARGETED PAIN THERAPIES

To help combat the nation's opioid epidemic, FDA is promoting a more tailored approach to developing and testing effective analgesics, with the aim of bringing less addictive pain treatments to market more quickly. This is part of a range of strategies for reducing excessive opioid use and misuse, while ensuring patient access to effective treatments for pain and addiction.

FDA's latest step involves issuing a series of guidance documents that map out specific methods for developing more targeted pain and addiction treatments, including abuse-deterrent opioid formulations and analgesics with low- or no-opioid formulations. To set the stage, FDA is withdrawing a 2014 draft guidance on developing drugs and biologics with analgesic indications, explained FDA Commissioner Scott Gottlieb in a recent statement. The old advisory will be replaced by at least four new guidances in the coming year that aim to shift sponsors away from development programs with multiple large studies designed to support new products with broad indications for treating general chronic pain.

The new advisories will recommend that sponsors study one or two populations with an eye to gaining more expeditious approval of drugs or biologics that treat specific kinds of pain in certain patients. An initial guidance will encourage using this approach in developing low-opioid pain therapies that "demonstrate clinically meaningful reduction" in exposing patients to opioids in treating acute pain. Another document will provide a new framework for evaluating risks associated with the intentional misuse or abuse of new opioid therapies. A third guidance will support the development of extended-release local anesthetics to replace oral systemic opioids in certain situations.

— Jill Wechsler

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This webcast discusses the key differences and responsibilities of data monitoring committees (DMCs) and clinical endpoint committees (CECs) and how sponsors can best determine what type of study oversight is appropriate—and for CROs, how to effectively navigate the complexity of appointing a committee.
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In a four-part series to date, discover the key findings and results from the Center for Information and Study on Clinical Research Participation's (CISCRP) landmark 2017 Perceptions & Insights Study, which included 12,427 respondents across pharma and biotech companies, CROs, and sites.
https://bit.ly/2NPSIfR

Find out what it takes to build strong partnerships and advance clinical research in this CRO industry survey, conducted by SCORR Marketing and *Applied Clinical Trials*.
http://bit.ly/2yDxie6

NEWS NOTES

PhRMA: R&D INVESTMENTS FOR MEMBER COMPANIES HIT RECORD HIGH IN 2017

Member companies in the Pharmaceutical Research and Manufacturers of America (PhRMA) invested $71.4 billion in research and development in 2017, the highest level of investment on record, according to the 2018 PhRMA member annual survey (see https://onphr.ma/2oFQpRT), released in conjunction with the 2018 Biopharmaceutical Research Industry Profile (see https://onphr.ma/2wJoC7w).

R&D intensity at PhRMA member companies remains consistently high as well: In 2017, about one out of every five dollars of revenue was devoted to R&D. Additionally, PhRMA member R&D spending represents the majority of the estimated $90 billion spent by the entire U.S. biopharmaceutical industry on R&D in 2016. The U.S. biopharma sector at large accounts for roughly one-sixth of total domestic R&D spending by U.S. businesses, the single largest share of all U.S. business R&D.

Among potential medicines in clinical development, 74% are potentially first-in-class. There are currently more than 1,100 new medicines and vaccines in development to treat cancer. Last year, the FDA approved the first gene therapies, the first medicine for primary progressive multiple sclerosis, and the first treatment for sickle cell disease in 20 years.

Novo acquires glucose company

Unit DX, a scientific incubator in Bristol, U.K., announced in August that its anchor tenant, Ziylo, has been acquired by big pharma Novo Nordisk A/S in an agreement that could exceed $800 million. Ziylo's technology platform offers the potential to develop glucose responsive insulins (GRIs), a novel treatment for diabetes patients.

The acquisition gives Novo Nordisk full rights to Ziylo's glucose binding molecule platform to develop GRIs. The development of this technology is a key strategic area for Novo Nordisk in its effort to develop this next generation of insulin, which could lead to a safer and more effective insulin therapy. A GRI would help eliminate the risk of hypoglycemia, the main risk associated with insulin therapy and one of the main barriers to achieving optimal glucose control. A GRI could also lead to better metabolic control and thus reduce the overall burden of diabetes for people living with the disease.

Lung disease research alliance

Antidote, a digital health company, and phaware, an advocacy organization dedicated to creating global pulmonary hypertension (PH) awareness, have struck a strategic partnership that will provide comprehensive patient recruitment services to pharmaceutical companies and CROs running trials in chronic lung diseases. The new alliance combines phaware's patient engagement model with Antidote's end-to-end clinical trial recruitment methods to accelerate medical research for PH and related diseases by driving recruitment efficiencies in these rare conditions. The acceleration of research in PH is critical. While 14 treatments for the condition have hit the market since 1995, there is only one approved for children.

Regeneron inks cell therapy pact

Regeneron Pharmaceuticals, Inc. and bluebird bio, Inc. have entered into a collaboration to apply their respective technology platforms to the discovery, development, and commercialization of novel immune cell therapies for cancer. The collaborators will specifically leverage Regeneron's VelociSuite platform technologies for the discovery and characterization of fully human antibodies, as well as T cell receptors (TCRs) directed against tumor-specific proteins and peptides. Bluebird will contribute its expertise in gene transfer and cell therapy.

Peptide therapy collaboration

IRBM, an independent partner research organization in Italy, has formed an agreement with Merck & Co., known as MSD outside the U.S. and Canada, in which IRBM will apply its expertise in phage display peptide library design and screening and in chemical peptide synthesis and optimization, to identify potential peptide leads for a specific Merck clinical target.

— Staff and wire reports

CLINICAL TRIAL ENROLLMENT

SITE MODELS OF THE FUTURE: FINDING PATIENTS FASTER

The overriding theme in clinical development is "get medicines to the patients faster"—and to that end, many different ideas are in the mix. One of the most significant is this evolution around the patient. To get approved medicines to patients in a clinical trial, you have to find the right patients. Many of the new solutions evolving to meet this need address patients at the site level.

At the DIA Annual Meeting in June, Christian Burns, vice president of BTC Network and ClinEdge; Sean Stanton, president and CEO at LifeCore Solutions; and Jennifer Byrne, co-founder and CEO of the newly launched Javara (see: https://bit.ly/2PzGRmE) presented "Rebuilding or Building a Research Site in the Year 2020." During the session, they presented five site models and led the audience through an interactive discussion on how each of these are evolving to meet specific challenges. The models include virtual sites; specialty practice with research extension; dedicated research sites; large multi-physician health systems with research embedded; and academic sites. The audience discussed the pain points around each model as follows:

Specialty practice pain points

- Physical space to conduct and house trials because of fast growth.
- Centralized monitoring, audit trails, monitoring schemes, paper source, QC.
- Investigators/training/getting physicians interested and aware of the research they offer.
- Differences in standard of care nursing vs. research coordinators.
- Physician time to invest in research, like everywhere burden with reps, time with patients, and EHR.

Large multi-physician practices pain points

- Sponsors label migraine study as neurology, so the study doesn't go to the right physician group, i.e., primary care would see more migraine than neurology.
- Engaging communication and feasibility of the practices throughout the system.
- Getting to the C-suite with a solution.

SITE-LEVEL STRATEGIES

MODEL	INNOVATOR	WHAT THE MODEL DOES	HOW IT DOES IT	PARTNERS
Virtual	Science 37	Decentralized, virtual model that goes direct to patients.	Uses Network Oriented Research Assistant (NORA); in-house experts handle patient questions.	Eli Lilly, Novartis, Sanofi, Genentech, Philips Healthcare
Specialty practice with research extension	Elligo Health Research	Brings clinical trial expertise to specialty physician group practices.	EHR and platform to find patients within the provider's network. In-house experts are responsible for clinical trial operations at the site.	Advarra, Allscripts, Consorta Health, Greenleaf Health, Saama Technologies, Society for Clinical Research Sites (SCRS)
Dedicated research site	Circuit Clinical	Integrated research organization (IRO). Clinical research program embedded in the practice.	Participant platform for education and to find clinical trials. Match trials to the physician's interest.	Physicians
Large multi-physician health systems with embedded research	Javara Research	Integrated research organization (IRO) for large health systems. In-house experts coordinate and conduct clinical research with physicians within the continuum of care.	Standardized service platform.	Healthcare systems
Academic	Trial Innovation Network	Leverages the expertise and resources of the NIH's Clinical and Translational Science Awards (CTSA) program.	Goal is to create an academic home and an adaptive, sustainable infrastructure to support the Clinical and Translational Science Institute (CTSI) at the Univ. of Minnesota.	

Dedicated research site pain points

- Getting to community physicians to refer, recruit, and participate.
- Getting patients (still fear of placebo, education/awareness of clinical trials).
- Multi-vendor technology burden.
- Making payroll.

Due to the compelling topic and interest, the session didn't have time to delve into the virtual or academic space pain points. In the table above, SCORR Marketing, our market research survey partner, and *Applied Clinical Trials* wanted to focus on up-and-coming organizations that are driving innovation in each of the site models. Because of space constraints, we chose one for each, but, of course, we will continue to feature these innovators in upcoming articles in our pages and online.

— Staff report

LIFECYCLE MANAGEMENT

EU'S STATUS ON IDMP

The European CRO Federation, or EUCROF, recently posted Pharmacovigilance in 2020: Boldly Shaping the Future, an overview, Part 2: Identification of Medicinal Products (IDMP) Implementation (https://www.eucrof.eu/images/Documents/18-08-17-idmp-implementation_eucrof_pv_wg.pdf) developed by its Pharmacovigilance Working Group.

This paper follows another released last year, that offered insight into the increasing challenges of pharmacovigilance (PV) in the European Union (https://bit.ly/2MUDAlc). This paper addresses the worldwide effort of IDMP to harmonize medicinal product specifications across regulators and industry, and covers the whole lifecycle of a product from the lab onwards. Because the EU is the first region in the world to start implementing IDMP, this paper offers insights into the current state of IDMP in that region.

The authors first offer the explanation of IDMP as "the set of five ISO standards that are based on the HL7 standards for data elements, formats, and terminologies to uniquely identify and exchange information on medicines. Each standard describes different distinct elements of a pharmaceutical product." They offer a definition for each elements, as well as a helpful schematic to understand those elements.

The reason the IDMP falls under the PV domain is that it began as a tool to improve their safety activities, but the authors maintain that the scope has widened based on additional benefits expected with internationally harmonized IDMP adoption. Those benefits include, but are not limited to:

- Facilitating the identification and exchange of product and substance information globally, across regulators.
- Improving data integrity and reliability.
- Enabling reuse of data across different procedures and regulators.
- Faster product identification in case of withdrawal of products with the same active substance.
- Quicker and more efficient response to findings on manufacturing sites that have impact on the quality of products.
- Minimize incidences of repeat information submission to authorities in the context of regulatory applications.

The European Medicines Agency's (EMA) approach to implementing the ISO IDMP standards is based on four domains of master data in pharmaceutical regulatory processes: Substance, Product, Organization and Referential data (SPOR). Although there is no direct mapping between the four SPOR domains and the five IDMP ISO standards, SPOR data elements will cover all requirements of IDMP. The authors describe the four domains in the paper, as well as industry's role in regard to the four domains.

While the EMA has issued its intentions around IDMP, industry is not without its duties, as just mentioned. For example, "all the data available to an organization that are associated with medicinal products should be identified, restructured, organized, and finally streamlined with the standard definitions, as they become available/published." The working group authors lay out a series of general steps that companies should follow in order to implement IDMP, noting that "a key element for a successful IDMP project is a comprehensive data source identification."

As far as timing for global implementation, in the EU, submissions of IDMP data will become mandatory most likely by the end of 2018 or beginning 2019.

— The EUCROF Pharmacovigilance Working Group

DEALMAKING

SYNEOS ACQUIRES CONSULTING AND OUTSOURCING COMPANY

Syneos Health, Inc. a biopharmaceutical solutions organization, has acquired Kinapse, an advisory and operational solutions provider to the global life sciences industry, from Hg, a specialist investor based in the U.K.

Established in 2005, Kinapse delivers services across the clinical and commercial lifecycle, and will further enhance Syneos Health's ability to provide customers with end-to-end solutions to accelerate time to market. Kinapse's capabilities expand Syneos Health's regulatory, safety, and pharmacovigilance consulting and operations in the post-market arena—outsourcing areas expected to experience double-digit growth. Additionally, the acquisition deepens the scale and scope of Syneos Health's clinical trial transparency, medical writing and quality operations, and consulting capabilities in the areas of R&D and clinical operations, medical affairs, market access, and quality and compliance.

Kinapse works with small to mid and large biopharmaceutical companies—including many of the top 20 global biopharma companies—and has more than 600 employees across the U.K., India, and the U.S. The acquisition increases Syneos Health's Asia-Pacific operational and delivery capabilities and doubles the company's consulting footprint in Europe. Kinapse operations will be integrated into Syneos Health's consulting business. The consulting arm drives connections between Syneos's core clinical and commercial offerings to optimize product launch and commercialization results.

"As customers increasingly face risk, competition, and rising development costs, the innovative, technology-enabled solutions provided by Kinapse are seeing increasing demand," said Alistair Macdonald, CEO, Syneos. "Through this combination we continue to inject new and enriched high-value solutions into the industry's only end-to-end offering, unlocking value for all of our biopharmaceutical customers."

— Staff and wire report

PATIENT ENGAGEMENT

DESIGNING AND EXECUTING A GENE TESTING COUNSELING AND DISCLOSURE PROCESS

In our world of clinical trials, disclosure of a person's genetic susceptibility to major diseases such as Alzheimer's is not only a potentially life-changing experience for the person and their family, but is also becoming a critical component for the design and development of countless future research trials for many diseases.

Genetic testing and disclosure has become particularly crucial for us because the Alzheimer's research paradigm is shifting, with scientists now focusing their efforts on identifying high-risk individuals *prior* to clinical onset of the disease. Our genetic disclosure program is helping us further study the impact of learning about a genetic risk factor for a disease that currently has no treatment or cure. And we have developed a testing and disclosure model that appears to be working effectively in dealing with this complex challenge.

As part of the Alzheimer's Prevention Initiative (API) Generation Program, we are identifying cognitively healthy individuals ages 60-75 who are at high risk of developing symptoms of Alzheimer's because of their age and because they carry either one or two copies of the e4 type of the apolipoprotein E (APOE) gene, the major genetic risk factor for late-onset Alzheimer's disease.

Because our prospective participants are required to learn their APOE genetic test results, we developed the API Genetic Counseling and Disclosure Process (GCDP) to determine the most efficient and effective way to incorporate both genetic counseling and disclosure into the screening process to maximize potential participants' psychological readiness to receive results prior to disclosure of APOE genotype.

Results from an earlier study, Risk Evaluation and Education for Alzheimer's Disease (REVEAL), published in *The New England Journal of Medicine*, showed us that the disclosure of APOE results was generally safe and did not trigger short-term psychological risks. However, there are two important distinctions between REVEAL and the Generation Program:

1. Participants in the REVEAL study were younger than those in the Generation Program, thus making them further away from their age of risk, and years away from their chances of developing Alzheimer's.
2. The REVEAL study included a smaller number of people with two copies of the e4 type of the APOE gene.

A traditional genetic counseling and disclosure model consists of multiple in-person visits, including a pre-testing educational counseling session, a testing component which can sometimes be combined with the first visit, and a post-testing counseling refresher and disclosure. However, for the Generation Program, we needed to design a process for counseling and disclosure that could be implemented in the context of our trials and could be adaptable and scalable for implementation across numerous sites in various countries. In addition, they needed to be based on varying local laws and regulations, differing referral sources, and varying degrees of knowledge among participants about their genetic vulnerability.

We use a modified design of the traditional genetic counseling and disclosure model to streamline the screening process, including three main components:

1. A pre-disclosure educational video and an educational handout that are typically included in a pre-testing educational counseling session and that inform participants about Alzheimer's, APOE, and considerations for learning their APOE results. These materials are available to prospective study volunteers prior to deciding whether to participate in the Generation Program.
2. APOE testing via a cheek swab to assess a potential participant's genetic risk for the disease. (Note: some participants have already provided a sample through GeneMatch, a program that matches healthy volunteers to Alzheimer's prevention studies based in part on their genetic profile, or through direct-to-consumer genetic testing. But if not, a sample is collected as part of the study.)
3. A counseling and disclosure visit that is completed remotely using telegenetics or through a local provider.

To assist in clearly and safely communicating genetic information, a risk-disclosure handout, guided talking points, and genotype-specific summary sheets are used as part of the disclosure process. Participants are also assessed in terms of their level of genetic knowledge, psychological wellbeing, health behaviors, impact of disclosure, and satisfaction with disclosure at multiple timepoints following the disclosure session to examine the ongoing impact of learning their APOE results.

Given the number of study sites and the limited availability of genetic counselors, we knew it was not possible to have all potential participants meet face-to-face with counselors to learn their genetic information. Therefore, we incorporated an ancillary sub-study—CONNECT 4 APOE—which utilizes telemedicine to deliver testing results either via telephone or videoconference. Through this effort, we are comparing the tolerability of each method to inform our program and future research efforts with the goal of helping to inform the development of scalable delivery models in the future, as well as insight toward the clinical implementation of APOE genetic testing for Alzheimer's disease risk assessment.

Many providers and study sites in the U.S. and around the world do not have experience with disclosure of APOE results, so the API GCDP provides an effective method for structuring genetic counseling and disclosure and for facilitating clear and consistent communication of genetic information in global clinical trials. Generation Program study sites have expressed high satisfaction and appreciation for the GCDP. We are gaining valuable information about how to effectively and efficiently disclose genetic information and how to make this process adaptable for studies with varying populations and country involvement. The information we are collecting will allow for ongoing refinement and improvement of the API GCDP for design of genetic disclosure in future studies.

—Jessica Langbaum, PhD, is Principal Scientist at Banner Alzheimer's Institute and Associate Director of the Alzheimer's Prevention Initiative

Bridging Research and Clinical Care

Insights on the challenges, activity, and motives in merging the two areas

Lisa Henderson

THE CARE CONTINUUM

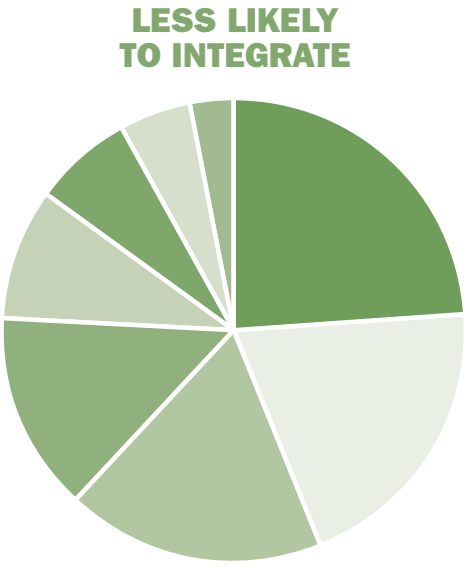
This past March, our survey partner SCORR Marketing launched its first conference called Bridging Clinical Research & Clinical Health Care (https://www.bridgingclinical.com/). The event highlighted the need, as well as the avenues taken by the presenters, on clinical research as a care option, which brings research closer to patients in the care continuum. The event broke down sessions into Technology, Regulatory, Patients, and Processes, and covered the myriad of challenges and opportunities for organizations to start thinking outside the box in each of these areas to meet this greater need in the overall healthcare system.

Over the summer, *Applied Clinical Trials* and SCORR Marketing took the core focus of the event closer to our audience with the Bridging Clinical Research and Clinical Health Care survey. The response to the topic was very positive, and top top-level insights on the respondent data are shared ahead. The full report is downloadable here: www.appliedclinicaltrialsonline.com/bridging-research-and-clinical-care-september-2018

The inherent flaw with this survey, of course, is that it was only distributed to a clinical trials audience. Therefore, there would be a bias toward the interests and ideas related to this industry vs. healthcare. If we were to poll a healthcare audience, we may have received a different perspective. Suffice to say, most respondents are aware that both clinical research and healthcare are very entrenched in their procedures and ways of operating. In addition, the clinical trials arena has a higher-level of regulatory scrutiny in regard to pharmaceutical drug development.

Almost half of the survey respondents were director level and above, and the other half manager and below, so there was a balanced representation between the decision-makers and those executing at the day-to-day functional level.

Moving to the Process piece, respondents felt that the greatest challenge in strengthening the connection between clinical research and care lay with gaining buy-in from healthcare providers, with 30% believing so. This is echoed in the chart above, which found hospitals and physician practices/networks the top two least likely organizations to work on integrating care. The outlier would be integrated delivery networks, which are larger regional



The response breakdown to the survey question: "Which of the following types of organizations are least likely to work on integrating clinical research and clinical healthcare?" Note: "Other" included smaller hospitals and health systems located in rural areas.

health systems that incorporate hospitals, practices, and community health services. The next two leading challenges cited by respodents in strengthening the connection between clinical research and care were improved integration between the clinical research and clinical care groups, at 28%, and developing patient-centric practices, at 18%.

There are potentially many avenues to address these challenges, through formal for-profit collaborations, or informal one-off collaborations, for example. Though we didn't inqure about profit motive in the survey question, 42% of respondents said their organization has an initiative to increase collaboration between research and care. Another 14% are in the planning stages, 32% are not planning at all, and the remainder are unsure of their company's plans.

METAMORWORKS/SHUTTERSTOCK.COM

Developing standards for electronic health records (EHR) was cited as the biggest challenge in integrating clinical research and healthcare data.

However, if industrywide incentives were offered in certain areas, respondents said on a scale of 1-10—most scored at an 8-9 or almost equally—that the following would encourage the integration of clinical research and clinical care:

- Data sharing
- eConsent simplification
- Education and training for physicians and patients
- Multisite institutional review boards (IRBs)
- Patient participation in clinical trials
- Physicians referring patients into clinical trials
- Stakeholder collaboration

The first two choices above are related to technology, so how did respondents rate technology required or used to bridge clinical research and clinical care? On a scale of 1-10, respondents rated that their company's investment in IT infrastructure to achieve healthcare interoperability at a 6. And while much is made of mHealth to improve patient engagement, facilitate remote data collection in trials, and enable more patients to participate in research for less on-site visits, only 26% of the respondents said their trials incorporated wearables or devices. The majority (58%) said their studies did not include those technologies, and the remainder were not sure.

To the question, "How does your organization currently use digital technology and data in clinical trials?" respondents answered:

- To coordinate source documentation for regulatory body compliance; 47%
- To identify eligible patients for studies; 45%
- To reduce time from data acquisition to data reporting; 44%
- To monitor real-time performance of sites; 36%
- To make it easier for patients to participate; 32%
- To design studies for patients; 25%
- To simplify physician referrals; 21%
- None of the above; 14%
- To leverage artificial intelligence; 13%

Clearly, the winner in a more integrated clinical research and clinical care ideal would be to simplify physician referrals, make it easier for patients to participate, and to more easily identify the right patients for studies.

> The greatest challenge in strengthening the connection between clinical research and care is gaining buy-in from healthcare providers.

Finally, much also is made of integrating electronic health record (EHR) data into the electronic data capture (EDC) record or vise versa. That area, in our survey, represented the biggest challenge in strengthening the connection between clinical research and clinical healthcare data. Developing standards for EHRs and EDC came in at 28%, ensuring data security at 23%, and developing data mapping tools for EHRs and EDCs at 22%. You can view more regarding the EHR and EDC topic here: http://www.appliedclinicaltrialsonline.com/how-ehrs-facilitate-clinical-research

The survey also included information regarding protocol design, degree of involvement and progress on education and initiatives around research and care integration, and the benefits of increasing collaboration, so we encourage you to download the survey.

Clinical Trials In a Dish: A Revolution Begins

Kevin P. Coyne, Shawn T. Coyne, Bernard Fermini

The emergence of CTiD offers the potential to remove future clinical failures much earlier in the process—and pave way for gains in R&D productivity.

EARLY PHASE DEVELOPMENT

While it is well known in the pharmaceutical industry that approximately 90% of drugs fail the clinical trial process, few have focused on the underlying driver of the high failure rate—because until now, nothing could (ethically) be done about it. Specifically, every person responds uniquely to every drug, with respect to both toxicity and efficacy, but preclinical testing, (including *in vitro* and *in vivo* animal assays) is currently engineered exclusively at determining a drug's effects on the average human, not on examining the distribution of impact across a target population. There has simply been no platform for testing a drug's impact on a human population prior to actual clinical trials.

But times are quickly changing via a new process, termed Clinical Trials in a Dish (CTiD). In the past 18 months, a number of published academic studies[1-5] have demonstrated that, when a scientist extracts a tissue sample from a specific human donor, converts it into a stem cell, and then differentiates that stem cell into either a heart cell (cardiomyocyte) or a liver cell (hepatocyte), the resulting cell is not simply a generic person's cell. Rather, that cell responds to drugs in the same way as that specific donor's actual heart or liver responds. This discovery enables researchers to conduct CTiD, using cells derived from cohorts of humans that are representative cross samples of target populations. CTiD can show, *in vitro*, the distribution of incidence and severity of toxicity that a candidate compound will likely display, *in vivo*, when exposed to humans during clinical trials. This enables pharmaceutical companies to terminate, very early in the development process, compounds that look safe when treating an average person but are unsafe for a portion of the population.

Importantly, CTiD are no longer just a theoretical possibility. In January of this year, Coyne Scientific began offering preclinical toxicity testing services utilizing a commercial application platform that uses a panel of donors selected to mirror the U.S. population. The company is nearing a completion of a joint development project with a large pharma company, the results of which will be published later this year. In addition, it is preparing for similar joint projects with two other big pharma organizations and is in discussions with still more.

Eliminating doomed candidates

How will CTiD change drug development? While it's tempting to conjure visions of a utopian time when animal trials and even human clinical trials are no longer required, such changes are years, perhaps decades, away. However, as a recent article in *SLAS Discovery* points out[6], CTiD can radically affect drug development immediately, without any changes in FDA regulations.

First to be affected will be preclinical toxicity testing. As pointed out, removing future clinical failures from the pipeline much earlier in the process can lead to significant improvements in R&D productivity. Cardiotoxicity is being addressed first but given the above referenced findings in scientific literature, hepatotoxicity should be addressable within a few years. After that, neurotoxicity and developmental toxicity will follow. Together, these four sources account for over 70% of toxicity-related clinical trial failures—which translates to nearly 30% of all failures. Eliminating the doomed candidate drugs much earlier in the process and focusing on the remaining 70% of candidates demonstrating a higher likelihood of clinical success, could improve the industry's R&D productivity by as much as 40% in the coming years. Some of that value may be strictly monetary, such as avoiding paying per-patient fees and expenses associated with clinical trials that are

destined to fail. But even more value can be realized by redeploying resources away from those compounds to those that may still prove beneficial, thus directly improving R&D productivity.

In time, CTiD will also be used for efficacy testing against cohorts of stem cell-derived tissues from diseased patients to determine those patient cohorts that may benefit from a candidate drug. Such tests will take more time to pervade the various therapeutic classes, because they require the ability to create the specific tissues to be targeted by a drug (and science has not yet developed the ability to differentiate stem cells into every type of tissue), and the tests must be specific to each class of remedy. But scientists are already using cardiomyocytes from diseased patients in efficacy testing[7,8]—and the leap from single-donor testing to cohort testing should not be far behind.

As soon as large pharma companies become comfortable with CTiD as part of the normal development funnel for their internal drug candidates, they can be expected to also consider such tests as part of the review package used when considering in-licensing of compounds from smaller developers. Today, the safety packages from smaller firms often contain limited information about the safety and toxicity profiles of the drugs, leaving the risk to the acquirer. Given that CTiD can be carried out in a few weeks, the acquirer can feasibly request such tests as part of any due diligence process. This shifts the risk of failure to the seller—with potentially profound impact on the entire ecosystem of the venture capital-backed, small-company drug discovery and development industry.

Looking more broadly, CTiD, when compared to actual clinical trials, possess the twin virtues of avoiding risk to living humans and also being far less expensive to conduct. This opens the doors to testing certain vulnerable populations, as well as populations for whom clinical trials are simply economically infeasible. For example, over half of many new drugs are consumed by geriatric patients (who often have different responses than younger adults), but this population segment is generally excluded from clinical trials due to problems with comorbidity, communications, compliance, transportation issues, etc. Comparative CTiD (comparing cohorts of older versus younger adults) could help answer the question, "Are geriatric patients at a higher risk of adverse events with this drug when compared to the population that was recruited for clinical trials?" And thus potentially avoid the cost, risk, and feasibility issues of a geriatric-specific clinical trial. The same concept could be applied to pediatric testing, or to provide predictions for bridging studies (e.g., the entry of a U.S.-approved drug into Japan) prior to incurring the expense of the actual clinical bridging studies.

Finally, consider the role CTiD could play in preventing adverse drug-drug interactions (DDIs). DDIs are difficult to study in the clinic, because (1) there are too many compounds that might regularly be coprescribed with the compound of interest to test them all individually, much less in multi-drug combinations; (2) there are ethical concerns with exposing patients to multiple drugs simultaneously, when each of the drugs has been individually shown to be potentially toxic; (3) each volunteer's usefulness is exhausted after a single combination of doses, whereas DDIs must be understood across every combination of therapeutic doses of the multiple drugs that might be prescribed; and (4) given that every person responds differently to each drug separately, we must expect that DDIs also vary widely across a population—so testing a small number of people at any one-dose combination does not provide an adequate understanding of the potential effects in a population. These problems simply cannot be overcome in a clinical trial setting—but they can be overcome through CTiD.

CTiD, when compared to actual clinical trials, possess the twin virtues of avoiding risk to living humans and also being far less expensive to conduct.

In the long run, it's likely that sufficient evidence will be compiled regarding the effectiveness of CTiD at predicting the toxic or beneficial effects of compounds in the clinic that this new tool can begin displacing animal testing (and even, eventually, early clinical trials). But the initiation of a revolution in drug development does not depend on such long-run outcomes—in fact, the revolution has already begun.

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References

1. Burridge, P. W.; Li, Y. F.; Matsa, E.; et al. Human Induced Pluripotent Stem Cell–derived Cardiomyocytes Recapitulate the Predilection of Breast Cancer Patients to Doxorubicin-Induced Cardiotoxicity. *Nat. Med.* 2016, 22, 547-556.
2. Stillitano, F.; Hansen, J.; Kong, C.-W.; et al. Modeling Susceptibility to Drug-Induced Long QT with a Panel of Subject-Specific Induced Pluripotent Stem Cells. *Elife*. 2017, 6, 1–24.
3. Shinozawa, T.; Nakamura, K.; Shoji, M.; et al. Recapitulation of Clinical Individual Susceptibility to Drug-Induced QT Prolongation in Healthy Subjects Using IPSC-Derived Cardiomyocytes. *Stem Cell Reports*. *2017*, 8 (2), 226–234.
4. Matsa, E.; Burridge, P. W.; Yu, K. H.; et al. Transcriptome Profiling of Patient-Specific Human IPSC-Cardiomyocytes Predicts Individual Drug Safety and Efficacy Responses In Vitro. *Cell Stem Cell.* 2016, 19 (3), 311–325.
5. Choudhury, Y.; Toh, Y. C.; Xing, J.; et al. Patient-Specific Hepatocyte-like Cells Derived from Induced Pluripotent Stem Cells Model Pazopanib-Mediated Hepatotoxicity. *Sci. Rep.* 2017, 7, 41238.
6. Available online at: http://journals.sagepub.com/doi/full/10.1177/2472555218775028.
7. Sun, N.; Yazawa, M.; Liu, J.; et al. Patient-Specific Induced Pluripotent Stem Cells as a Model for Familial Dilated Cardiomyopathy. *Sci. Transl. Med.* 2012, 4 (130).
8. Liang, P.; Sallam, K.; Wu, H.; et al. Patient-Specific and Genome-Edited Induced Pluripotent Stem Cell–Derived Cardiomyocytes Elucidate Single-Cell Phenotype of Brugada Syndrome. *J. Am. Coll. Cardiol. 2016*, 68 (19), 2086–2096.

Leveraging Modeling & Simulation in Oncology

Julie Bullock, PharmD, Marc Pfister, MD, FCP

How the use of M&S in cancer trials from the outset can help address those critical "what if?" scenarios and accelerate oncology drug development.

EARLY PHASE DEVELOPMENT

Insights from modeling and simulation (M&S) can help to overcome critical challenges associated with oncology clinical trials, by quantitatively integrating knowledge and relationships between the disease, drug characteristics, patient populations, and clinical trial parameters. M&S is used to fill in gaps related to limited data and extend the findings from existing trials for different scenarios and expanded patient populations. Such effort produces deeper understanding of a drug candidate's efficacy and safety profile and can help to streamline the clinical trial and drug development process, thereby reducing patient burden, risk of failure, and time to market.

A variety of challenges compound oncology drug development. They include:

- Patients with cancer who are enrolled in clinical trials are often already very sick and typically have comorbidities and numerous comedications.
- For some targeted therapies, clinical trials must enroll only patients with a specific oncologic profile, such as the presence or absence of a desired genetic mutation or other biomarker.
- Most oncology drugs are cytotoxic or genotoxic, and thus cannot be studied in healthy volunteers; similarly, targeted agents that can be studied in healthy volunteers may be limited in dose due to potential toxicities.

Meanwhile, to reduce the patient burden, and streamline the drug development and regulatory approval processes, many oncology clinical trials are limited in scope and duration, and single-arm clinical trials are often leveraged to gain initial accelerated or conditional approval from regulators. This approach limits which patient subpopulations and doses are evaluated in the trial setting—leaving sizable gaps in understanding for drug investigators and regulators. While this approach can speed patient access to the new therapy, it also puts added pressure on investigators, and highlights the importance of M&S tools that can produce greater insight from the limited available trial data.

Today, there is increased acceptance of M&S results and growing encouragement from regulatory agencies to use M&S tools. FDA Commissioner Scott Gottlieb recently included "the more widespread use of modeling and simulation, the greater use of real-world evidence in the pre- and post-market setting, and the adoption of better tools for collecting and evaluating more real-time safety information after products are approved" among the new scientific domains that have been introduced into the development and review process. Furthermore, the European Medicines Agency (EMA) just upgraded the reach of M&S within that agency.

Specifically, advanced M&S approaches continue to improve oncology clinical trials by helping investigators to:

- Plan, inform, analyze, and extend clinical trial data and conduct standalone virtual trials to provide supplemental understanding, taking into account inherent patient-to-patient heterogeneity in terms of their response to therapy and tolerability to treatment.
- Develop objective response data to show how drug-mediated, tumor-growth inhibition impacts both overall survival and other relevant surrogate endpoints (such as objective response rates, progression-free survival, disease-free survival, and patient-reported outcomes).
- Quantitatively evaluate and compare the efficacy-

safety profile of a new drug against the standard of care or other existing treatment options.
- Assess go/no-go decisions, support comparator-effectiveness studies, and streamline regulatory filings.

Fine-tuning dose determination

Poor or ill-informed dose selection is often to blame for failed trials, delays, and denials of regulatory submissions, and changes in dosing post-approval. M&S is being increasingly leveraged to improve dose escalation and determination of first-in-human (FIH) doses, to predict and analyze variable dose-response, and to optimize dose-regimen decisions—more broadly and more comprehensively than is possible using the traditional approach of hypothesis testing in a limited trial setting. M&S can be used to both interpolate and extrapolate existing trial data related to specific tested doses, compare with existing treatment options leveraging publicly-available data from competitor compounds, and thus investigate other possible doses and dosing strategies without the need for additional human subjects or dedicated studies.

Historically, oncology drug development involving traditional cytotoxic agents relied on maximizing toxicity, using the maximum tolerated dose (MTD) as the key indicator for maximizing treatment efficacy. Today's newer biologic agents and immuno-oncology therapies are often able to provide an efficacious dose well before drug levels have become toxic. Thus, clinical trials for such novel oncology agents must work to identify optimal doses and dosing frequency below the MTD to achieve the needed efficacy with better tolerability for the patient. This considerably complex undertaking is greatly enhanced using M&S.

Managing drug-drug interactions

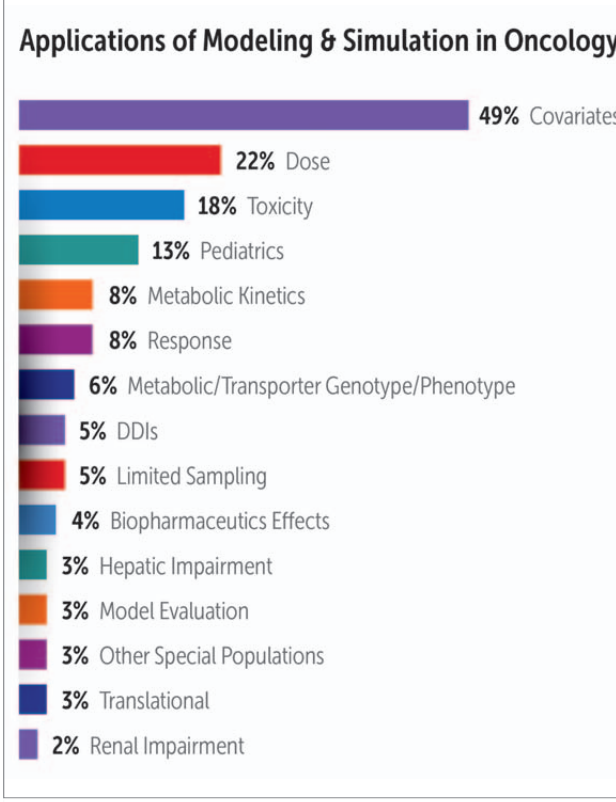
Due to polypharmacy, patients with cancer are at risk of multiple drug-drug interactions (DDIs) and it is impossible for clinical investigators to conduct an endless array of dedicated studies and trials to identify and understand all potential DDIs that may arise for a given oncology agent. Instead, investigators are increasingly turning to quantitative modeling techniques, which can produce rational, data-driven predictions about how the drug's absorption, distribution, metabolism, and excretion profile will impact different DDI combinations across many different simulated patient cohorts. The resulting insight can be used to inform drug labeling, and also help guide the inclusion or exclusion of patients taking DDI-implicated drugs during clinical trial design and post-marketing studies.

Today, promising work is also underway using modeling techniques to identify potentially advantageous DDIs—that is, specific combinations of investigational and approved drugs that may be able to improve clinical outcomes or tolerability.

Predicting drug activity in virtual patient cohorts

M&S lets investigators leverage relationships elucidated in the existing trial data to predict the drug-exposure impacts, clinical efficacy, and toxicity of investigational therapies in specific modeled patient sub-populations. For instance, such virtual patient cohorts may be structured by common variants such as age, gender, ethnicity, and weight, but also by more complex characteristics such as the presence or absence of specific genetic mutations or other biomarkers, specific comorbidities and coprescribed medications, organ impairment, and vulnerable patient groups (e.g., pediatric or geriatric patients and pregnant women).

Wide Reach



Source: Darwich A, et al. December 2017. Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs. *Translational Cancer Research*, 6(S10).

Using modeling to assess the competitive landscape

As the number of oncology agents continues to grow, drug developers must demonstrate not just how an investigational drug performs, but how it compares to other available therapies and those under development. Such comparative effectiveness studies typically look at how the investigational therapy stacks up in terms of clinical effectiveness and safety profile, and also potential complications, tolerability, dosing strategies, and potential DDIs—all factors that could reduce long-term adherence to therapy and clinical outcomes for patients.

Modeled and predicted results help to extend available data produced in actual clinical trials, and answer key questions about how the drug performs in larger, virtual patient populations. This helps to produce the strongest case for drug developers to present to regula-

tors and payers regarding how the drug is likely to perform in heterogeneous patients under real-world conditions.

The high cost and competitive landscape for oncology drugs have resulted in increased pressure from healthcare payers to justify adding the therapy to the formulary—another area for M&S, albeit related to health economics.

Today's modeling toolbox

Exposure-response and pharmacokinetic/pharmacodynamic modeling incorporate PK and PD data gathered during early- and late-stage clinical trials.

Exposure-response modeling is increasingly used to support optimal dose selection; provide proof-of-concept for the drug; elucidate and validate the treatment's mechanism of action; improve characterization of relationships between drug exposure, efficacy, and toxicity; and inform interpretation of risk-benefit profiles. Such insight is essential not only for dose justification (which relies heavily on establishing dose-response relations) but for regulatory labels where dose modifications may be required for specific patient populations to avoid adverse events.

Population PK modeling is used to leverage sparse concentration data and evaluate the variability of drug exposure across individuals in a population over time. Such M&S approaches can facilitate not just development of new treatments for adults but also streamline pediatric drug development programs.

Physiologically-based PK (PBPK) modeling helps to predict the drug's PK activity both in the body and the tumor site. PBPK models are built using preclinical and clinical trial data and can assess the therapy in simulated patient subpopulations to inform further clinical trial design and product labeling.

PBPK modeling is often use to predict DDIs but it can also extrapolate drug-function findings between patient cohorts, based on age and disease demographics and physiological differences (e.g., adult versus pediatric populations or cancer patients versus healthy volunteers). PBPK has gained significant traction with global regulators and PBPK-modeled results (in lieu of clinical studies) have been accepted by FDA to support more than 150 label claims.[1]

Quantitative systems pharmacology (QSP) combines computational modeling and experimental methods to examine the mechanistic relationships between an investigational therapy, the biological system, and the disease process. QSP models can help to elucidate how target exposure, binding, and expression occur in biological pathways, impacting disease determinants, drug efficacy, and disease progression. This allows for optimal combinations and dosing regimens to be explored within a virtual population. QSP modeling is also used to reduce Phase II attrition by enabling a wide range of "what-if" scenarios to be investigated—ahead of the actual clinical investigation—to optimize trial design.

QSP models are also being used to simulate biomarker responses for a drug or multiple-drug regimen across virtual trials, providing added insight that can help to inform ongoing trial design. Meanwhile, many researchers consider QSP modeling an essential element for successful immuno-oncology drug discovery, because the number of possible combinations (in terms of drugs and dosing schedules) is simply too numerous to explore experimentally.[2]

Model-based meta-analysis (MBMA) is used to compare the investigational therapy with other drugs being tested in clinical trials or on the market. MBMA-demonstrated superiority for the drug candidate provides ongoing encouragement for investigators. In contrast, demonstration of non-superiority allows the drug developer to either leverage the findings and fine-tune the design of ongoing trials, or revise corporate priorities (perhaps focusing limited resources on more-promising candidates). MBMA can help to understand expected response in control arms (e.g., against the standard of care), and to identify a dose that is expected to be associated with competitive efficacy and safety outcomes in clinical trials.

MBMA is also used to provide "virtual comparator" data, to put into context benefits seen in single-arm trials.

Tumor growth modeling aims to better characterize tumor-size responses to therapy to establish the optimal dose regimen and therapeutic window and allow use of that relationship as an early marker for survival. Several promising oncology products have received their initial approval on the basis of tumor size in response to therapy (objective response data)—rather than survival outcomes. This places further emphasis on developing a thorough understanding of tumor-size dynamics and the effects of investigational drug candidates on tumor growth or shrinkage. As a result, novel approaches to tumor-size modeling are being developed and applied to support both drug development and regulatory decision-making.[3]

Closing thoughts

The strongest development program makes maximal use of all available data at the outset, and then applies M&S to answer essential questions, explore "what if?" scenarios, fill in critical gaps, and assess how the investigational therapy works and is tolerated in expanded patient subpopulations and different scenarios to those evaluated in the clinical trial dataset.

There is a growing body of evidence in academia, industry, regulatory agencies, and health authorities that M&S can facilitate development, approval, and cost justification of oncology drugs. This trend will continue.

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References

1. PBPK Modeling and Simulation: Yesterday's Scientific Endeavor is Today's Regulatory Necessity. https://www.aapsnewsmagazine.org/articles/2017/dec17
2. "Model Firsts." p 1-6. *BioCentury Innovations.* August 2, 2018.
3. The Model-informed Drug Development Imperative in Oncology R&D. https://www.certara.com/wp-content/uploads/Resources/Booklets/BK_MIDDImperativeOncology.pdf

Genetic Testing in Clinical Trials: A New Level of Patient Centricity

Industry experts look at how the specific needs of patients come into play when conducting gene-based screenings.

At a panel hosted by WCG at the DIA Annual Meeting in June, *Applied Clinical Trials*' Editorial Director Lisa Henderson moderated a session entitled "Clinical Trials in the Era of Precision Medicine." The panel included Ken Getz, associate professor at the Tufts Center for the Study of Drug Development at the Tufts University School of Medicine; Jill Johnston, president, WCG's site activation solutions; Karmen Trzupek, director of ophthalmology and rare disease programs at InformedDNA; and Travis Quigley, VP for Clinical Development at bluebird bio. During the session, these experts discussed many aspects of genetics and clinical trials, but in this article, based on a transcript of the event, we focus on the very different needs that patients in clinical trials have in regard to gene testing.

As Getz set the stage for the attendees, he recalled the excitement over the mapping of the human genome, completed in April 2003. "We thought overnight we would have treatments that would target a specific patient with a specific genetic profile. And we talked about the incredible importance of genetic information to actually target our therapies, but it's taken a long time for that to influence our pipeline," said Getz. "We're really there at that time now."

He noted that half of all drugs across all therapeutic areas are collecting biomarker and genetic data. In fact, in oncology, that number is closer to 80%. In addition, almost half of all pharmaceutical companies are earmarking biomarker and genetic data as the most critical areas to increase investment.

Getz said, "With the changes to these very highly-targeted therapies for rare and orphaned diseases, it's introducing a host of challenges at the operating level. And it speaks to changes in the way we conduct our studies, in data that we collect, and how we interact with the patient community."

Both Trzupek and Johnston noted an increase in the use of genetic testing in clinical trials, including for diagnostic purposes, prognostic purposes, or predictive purposes, such as potential response to a treatment, inclusion in a clinical trial, or to stratify patients into more personalized trials.

Johnston believes that increased patient involvement in all aspects of clinical trials, such as prescreening tests or protocol design, puts other considerations in focus for genetic tests. "We need to think not only about just simply adding a genetic test to a protocol, but also thinking how is the patient being prepped for that type of genetic testing, what will the outcomes be? How are they progressing through the study? What other information do they need? And, so, really thinking about it from a high level, but also a very detailed level—what's going to happen with those particular patients?"

In developing bluebird's genetic-based therapies, Quigley said, "These challenges can also be daunting when you start doing these tests in trials. Some of the providers don't even want to know the results because they don't have the resources to successfully manage their patients' expectations and family expectations around what the results mean, and how it's translatable to the reality of developing any diseases later on. From the sponsor side is the challenge of what information we actually share, or what do we truly think actionable for patients? And to have the investigators or providers communicate to patients, how do we build the resources to help them do that? But that's a daunting task for a company who's not up to date on those things."

Said Trzupek, "A large part of [WCG and InformedDNA's] partnership and collaboration is exactly around supporting patients and their families. When discussing genetic testing, there is complexity of the actual result. That's something the genetic counselors at InformedDNA do every day and we spend a lot of time with the patients and providers doing that."

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What else should be considered for a patient-centric approach to gene testing?

Family members. In the area of genetic disease, there is a greater possibility that there is potential risk for the family of patients. Trzupek said, "The genetic counselors spend a lot of time with the patient, talking through all the downstream effects, both for their own healthcare and for potential risk to their family. Identifying that is a huge benefit to the patient, which increases engagement, but it's also often a benefit on the other side because you end up identifying other individuals in the family who may also potentially qualify for a clinical trial or a therapy, and they're often very grateful for that."

Negative screen results. What do you do if a patient screens "no" for that gene or variant? Johnston said, "Those patients are suffering some sort of condition, and they're looking for the next answer as well. You may not be providing deep genetic counseling for them, but they want education and information. And you don't want to lose their engagement in the future."

> Sponsors must be patient-centric in their approach in genetic testing because of the ethical responsibility and disclosure for the patient community.

Trzupek provided an example of what education would look like in this "screen no" scenario. "A classic example would be BRCA1 and BRCA2 in breast cancer," she said. "One of the most important components of genetic counseling for patients going through that testing is ensuring that women who screen no, who have a negative genetic test for that, don't erroneously think that they're no longer at risk for breast cancer. Across all diseases we see this, so we need to make sure the education is there."

Incidental findings. In the course of genetic testing, indicators may show the patient has a propensity for another disorder. How should that be handled? Trzupek said that genetic counselors spend a lot of time thinking through the ethical challenges of that scenario. In clinical trials, she suggested that sponsors be made aware very early on of what they want from genetic testing. "We have to talk about this early as it is critical to the trial design," said Trzupek. "How to be thoughtful about what test is being offered, how narrow or how broad is this test, and what are the potential implications? Do we have or need a plan to manage that?"

Quigley and Getz both shared that, at the end of the day, sponsors must be patient-centric in their approach in genetic testing because of the ethical responsibility and disclosure for the patient community. Quigley closed with, "In starting to think about the right collaborations with providers or healthcare institutions, we have to understand how we're going to handle all this data, and act on it moving forward, creating the right environment for patients to get the help they need to live healthy, stress-free, productive lives. It can also benefit the development of therapies for rare diseases. It takes a lot of people getting together, having conversations like this, and eventually taking that next step to create systems that can function to help everyone that's involved."

—Staff Report

A modified design for disclosing genetic test results in Alzheimer's research/see page 17

Challenging the 'Site-first' Status Quo in Patient Enrollment

Tammy D'Lugin-Monroe, Daniel Brunwasser

Case study highlights a new patient-centric enrollment model that uses a data-driven approach to identify qualified patients first.

The great operational challenge of clinical trials is to identify and enroll qualified subjects. This essential first step continues to be the point at which most studies stumble and may even fail. Historically, sponsors have relied on study sites to recruit and enroll patients, depending on sites to estimate the number of qualified patients they can access, and focusing on the selection of patient-rich sites to achieve enrollment targets.

Years of industry benchmarking have documented the limitations of this "site-first" practice, which typically leads to enrollment delays and follow-on increases in research time and cost.[1,2] Despite the efforts of sponsors and contract research organizations (CROs) to improve the selection of optimal investigative sites, all too often the result is low enrollment across a large number of sites, with most of them enrolling too few subjects.

Slow and insufficient recruitment leads to prolonged study enrollment, followed by the conventional "fix" of adding more sites and, often, adding sites in more countries. This further dilutes enrollment rates, driving up costs and delaying time to product approval. The fact remains that a site rich with a population of *potential* patients does not necessarily translate to *actual* enrollment of randomized study subjects.

In recent years, some improvements have been gained by leveraging electronic medical record (EMR) data to identify potential study participants. Although EMRs can alert caregivers to a potential subject within a medical dataset, that information must be referred to study investigators to translate into randomizations. Treating physicians, who are increasingly overwhelmed by "alert fatigue," lack time and motivation to act on growing numbers of EMR alerts to patient matches for a prospective study.[3]

Persistent failure to achieve enrollment on time and within budget is due in large measure to continued reliance on investigational sites for feasibility assessment and patient recruitment—practices that demand expertise and capabilities beyond their scope.

Sites routinely overestimate the numbers of patients they will be able to enroll, generating false positives that result in under-enrollment, the need for additional sites, and cost over-runs. The use of EMR and de-identified patient health claims data improves the identification and location of potential patients with a target disease indication. But only a subset of these populations actually will qualify for or be interested in participating in a specific study.

Increasingly complex study protocols make it more difficult to identify qualified subjects within a population of accessible patients, and there is more competition than ever for those patients who do qualify. For recruitment, sites still rely primarily on traditional methods—physician referrals, complemented by print, radio, and television ads—approaches that are increasingly inadequate in the crowded research landscape.

A better way: Put patients first

Sophisticated data mining, analytics, and social media are creating new platforms to conduct highly effective feasibility assessment and patient enrollment. To overcome the limitations of the site-first approach, PPD

developed a patient-centric methodology that randomizes more patients to fewer sites in less time by identifying qualified patients before selecting sites. The patient-first model depends upon the integration of PPD clinical trial services with those of Acurian, its enrollment affiliate, and the dedicated site network, Synexus.

This model was developed in the context of enrollment challenges facing clinical research in chronic ambulatory disease indications. Populations of potential study patients are abundant in asthma, diabetes, hypertension, atopic dermatitis, hyperlipidemia, osteoarthritis, and other prevalent, non-acute diseases. The difficulty is in identifying qualified and interested patients, and channeling them to selected investigational sites.

Strategic enrollment: Finding qualified subjects in a pre-screened population

Central to this model is the use of proprietary databases that enlist patients who express interest in research participation and who provide self-reported health and household information. Both the strategic enrollment consultant and the dedicated site network maintain and expand proprietary databases.

Database population. Proprietary databases used in PPD's model have amassed information on pre-screened patients across thousands of studies, retaining information for all patients screened, as well as for the smaller percentage of patients randomized to studies. Acurian's database currently holds information for 20 million pre-screened individuals and 100 million identified households across 70 countries. An estimated 10,000 people are added daily as strategic, multichannel advertising campaigns recruit great numbers of potential subjects for new studies.

Subject identification and modeling. Study-specific data mining and profiling begin with the identification of database members with the relevant disease indication. Patient-provided health information drives more targeted identification of subpopulations most likely to meet a given study's inclusion/exclusion criteria. Potential subjects are invited to contact recruiters through multiple channels—online, call-in centers, pre-screening visits—to learn if they quality.

To better understand this population of pre-qualified patients and increase confidence in randomization, interviews, surveys, and historic study data are leveraged to determine their interests and motivations in study participation and to identify potential barriers to enrollment. Targeted patient modeling takes into consideration criteria from clinical data and demographics to lifestyle attributes, online activity, and household purchasing patterns.

Feasibility and mapping. Based on the pool of pre-qualified patients, highly predictive, proven enrollment models are used to define the number of patients that can be enrolled for given study. Patient locations are mapped geographically to identify patient-rich areas most suitable for study sites. Geographical mapping also informs the best approaches for targeted advertising and the best communication channels to use in recruitment, which can vary dramatically by location.

Recruitment and engagement. In the patient-first model, recruitment goes hand in hand with patient engagement and education to communicate a clear understanding of study benefits and the commitment required of subjects. Pre-screened and pre-qualified subjects receive ongoing information on the purpose, value, and process of studies to build an informed and committed patient cohort, while improving retention.

Pre-qualified subjects are followed throughout the enrollment process, sharing their disease and treatment experiences and contributing their views and preferences related to study procedures. All of this patient intelligence is fed back into the database to inform subject identification for future studies.

> Increasingly complex study protocols make it more difficult to identify qualified subjects within a population of accessible patients, and there is more competition than ever for those patients who do qualify.

Social media also is used to connect patients directly to researchers and leverages self-reported patient data to locate and enroll patients who meet a subset of inclusion/exclusion criteria for a specific trial. After modeling and mapping locations, potentially qualified patients are channeled to high-performing study sites—network and non-network—matched to their locations.

Referral. Patient identification operations are closely integrated with enrollment conducted at the sites. Pre-qualified candidates are referred to appropriate sites using intelligent matching algorithms that can help improve program efficiencies by applying nested protocol logic and site staffing capacity.

Site selection: Benefits of a dedicated site network

Based on the qualified patient population identified from the databases, PPD defines the location and number of investigative sites required to meet enrollment targets. The model draws first from the nearly 200 dedicated and affiliated sites in the Synexus network, and then from additional top-performing traditional sites as needed. The global network of dedicated sites boosts efficiencies using shared processes and streamlined operations to ensure that regulatory submissions and other startup activities are completed by the time the first patients are referred. These Synexus sites pre-screen patients in anticipation of site activation, allowing for screening to commence immediately thereafter.

Recruitment and enrollment support. Synexus has a comprehensive range of recruitment methods to support study enrollment across the network of sites. Recruitment strategies and tactics are

monitored and adjusted throughout a study lifecycle to optimize the match of patient to site.

Face-to-face engagement. Site engagement strategy puts patients at the center of trial preparation and management. Each strategy is tailored to the specific circumstances of the patient community. All Synexus sites engage with primary care providers, specialists, and pharmacists to establish a network of healthcare professionals and integrate with the local health system to support study-specific requirements. Network sites conduct patient interest visits—non-study-specific encounters that introduce patients to the site and provide an opportunity for them to meet with a member of the medical team. Patients hear about the research process and the role of a study participant. These visits enable patients to make more informed, committed decisions about clinical research participation.

> Conducting all trial activities at dedicated research sites offers additional support for the patient-centric model. Patients can be managed throughout the lifetime of the study.

Global standards. Conducting all trial activities at dedicated research sites offers additional support for the patient-centric model. Patients can be managed throughout the lifetime of the study. Global standards, procedures, and training are in place at all sites, contributing both to high quality and to significant cost and time reductions across studies and entire development programs.

Global cholesterol study: Patient-first model reduces startup time

PPD's approach was used to accelerate enrollment in a global Phase III program to evaluate a lipid-lowering therapy. The program included three studies to be conducted in 13 countries across the U.S., Europe, and Africa. Target enrollment was 3,400 patients, and the sponsor needed to meet aggressive timelines: the goal was to screen the first subject no later than 3.5 months (107 days) after delivery of final protocol for the first study.

Synexus provided 83 of the 277 sites used in the three Phase III trials. Based on the patient-first identification methodology, PPD screened 5,299 patients in 114 days and enrolled 3,660 subjects in 126 days. Compared to industry benchmarks based on 2014 to 2016 trial performance data, the patient-first strategy reduced startup across the three studies and all 13 countries by 47%. The slowest-enrolling country (Sweden in study 1) reduced startup time by 24%, while the fastest-enrolling sites, in the U.S.-based study 2, reduced startup time by 88%.

In the first 30 days of the program, 39 investigative sites were activated, 390 patients were screened, and 115 patients were enrolled. Other acceleration measures, compared to industry benchmarks, include:

- First protocol received to first site active: 63% faster
- First site activated to last site activated (over three studies): 73% faster
- First subject randomized to last subject randomized (over three studies): 72% faster
- First protocol received to last subject randomized (over three studies): 62% faster

Aligning operations with patient needs

The value of patient centricity is increasingly recognized in drug development, but the term "patient-centric" is often more buzzword than methodology. A working definition, co-developed by patients, caregivers, and community advocates, characterizes patient centricity as: "Putting the patient first in an open and sustained engagement for the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family."[4]

PPD's enrollment model operationalizes this principle, leveraging in-depth patient information and insights to speed enrollment, minimize the number of study sites, and accelerate startup. The ultimate goal of patient centricity is to develop therapies more closely aligned with patient needs. The patient-first recruitment model demonstrates that patient-centric approaches also can address the needs of sponsors to reduce research time and cost.

References

1. Lamberti MJ, Chakravarthy R, Getz KA. "New Benchmarks for Trial Initiation Activities," *Applied Clinical Trials*. Dec 1, 2016. Available at: http://www.appliedclinicaltrialsonline.com/new-benchmarks-trial-initiation-activities?pageID=3
2. Tufts Center for the Study of Drug Development: Impact Report January/February 2013. "89% of Trials Meet Enrollment, But Timelines Slip, Half of Sites Under-enroll."
3. Chavis S. "Next-Generation Patient Recruitment for Clinical Trials," *For the Record*. 2017; 29 (10) 14-18. Available at: http://www.fortherecordmag.com/archives/1017p14.shtml
4. Yeoman G, Furlong P, Seres M, et al. "Defining Patient Centricity with Patients for Patients and Caregivers; A Collaborative Endeavour." *BMJ Innovations*. 2017; 3 (2). Available at: https://innovations.bmj.com/content/early/2017/03/24/bmjinnov-2016-000157

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The Future of Mobility and Medicine

Jonathan Palmer

The role of the cloud in realizing the practical benefits of mHealth in clinical trials.

PATIENT CENTRICITY

The phones we now carry have changed the way we connect with one another, find our way around, and decide where to have dinner or buy a movie ticket. The way we operate our homes has changed, too, whether it is turning on the alarm or adjusting the thermostat while we're away. Our connected cars, using GPS, stream our favorite tunes while we make our way through a smart city. This is the "Internet of Things," and it is becoming just as pervasive in the world of clinical trials. Call it the "Internet of Clinical Things"—which is rooted in mHealth, where mobility and medicine meet.

Ninety-four percent of pharmaceutical companies, contract research organizations (CROs), and service providers plan to increase their use of mHealth, according to research from KNect365. Why is that and what will it look like? Here are some possibilities.

1. Drugs are expensive to develop, but mHealth could bring the cost down

It takes more than a decade to advance a new drug to market, and an average cost of $2.5 billion, according to the Pharmaceutical Research and Manufacturers of America (PhRMA). Historically, clinical R&D consisted of many disjointed processes supported by isolated eClinical point solutions. The challenge with this scenario is that these solutions don't share data, processes, or validation, requiring study teams to re-enter data and treat each step in a clinical trial as an independent trial, versus a piece of a single, unified study. This "old way" protracts the development and approval of potentially life-saving drugs that could help patients waiting in need.

The rise of mHealth technologies, including mobile sensors, patient engagement apps, and telemedicine are reshaping the way clinical trial data is collected and could improve the efficiency of studies when combined with the cloud. The FDA approved AliveCor's Kardiaband, the medical device accessory for the Apple Watch. MC10, FitBit, Validic, CMT, MIR, Nonin, A&D Medical, and Possible Mobile are making important innovations to support mHealth. Streaming data from these and other eSources into a secure, central cloud-computing environment that intelligently interprets, aggregates, and distributes clinical data to clinical systems will give all trial stakeholders access to consistent and current participant information.

Gathering data in novel ways with mHealth, and storing it in the cloud, sharply reduces steps necessary to access data and better understand the safety and efficacy of investigational drugs. As a result, the industry can bend the cost curve down with mHealth.

2. Geography traditionally stands in the way, though mHealth could make trial locations agnostic

Patient recruitment is a persistent problem in clinical research. Many research centers are challenged to find and enroll sufficient numbers of clinical study participants, according to the Tufts Center for the Study of Drug Development (CSDD). Prospective participants, as well as their primary care doctors, remain unaware of the various clinical trials that are being conducted. Tapping into cloud data produced by mHealth sensors, including genetic information, could help find potential matches. In particular, being able to correlate biomarkers with physiological data could help identify a large enough population for a trial rapidly, in contrast to traditional methods, which could take years or not work at all.

Once they are enrolled in a trial, it's vital that patients adhere to the requirements—dosage amounts, frequency, and under what circumstances. Ensuring that compliance is the difference between a patient whose results can be

used in the study, and a patient whose results have to be discarded, costing the individual time and the sponsor/CRO time and money. A pill bottle sensor cap is an example of mHealth, in that it can generate data to provide evidence that patients did what they were expected to do.

Even if they are willing to take their medicine on time, many patients will quit a trial before it is completed (or never sign up at all) because of the associated travel and time commitments. mHealth technologies such as heart rate sensors, blood pressure devices, and even electronic diaries have led to the creation of so-called "site-less" trials that can make it much easier for patients to participate.

Conventional clinical trials require participants to travel to research centers on a regular basis for screening, to receive treatments, and for monitoring how they are responding to the investigational drug. The process includes routine screenings like blood tests, X-rays, or other diagnostics. In many cases, patients live two or more hours from the nearest research site, forcing them to disrupt their normal schedule, perhaps several times a month. It's this commitment that often compels patients to opt out of a trial.

With site-less trials, assessment and monitoring could occur in a patient's home or at a local clinic or hospital, where data captured via a device could be sent directly to the cloud for access by the site and clinical coordinators. Mobile devices would provide researchers with additional real-time, detailed data on patients between clinical visits as well, which can provide more information for researchers. For example, patients who are stressed by a long car ride to a site, and by the surroundings, may exhibit hypertension during their visit, possibly leading researchers to conclude it is a side effect of the medicine. But at home, without that stress, a sensor could show normal blood pressure. With the data in the cloud, clinical trial coordinators not only can keep a close watch on progress from afar, they also can analyze the data to tell the difference between a true side effect and an anomalous reading. That same adverse event (AE) data stored in the cloud can then be accessed by AE teams to comply with FDA reporting requirements.

MHealth, combined with the cloud, gives therapeutic teams a new opportunity to meet enrollment targets, options to gather data, and tools to improve adherence to study protocols. If we are able to expand the number of patients by expanding to more geographic regions, we have the power to increase the number of trials and, therefore, the possibility of bringing more life-saving therapies to market faster.

3. Evidence is required to prove the treatment works, and give more back to the patient

Data transformation and semantic interoperability—converting raw data into submission-ready data sets—are vital pieces of any clinical trial that will leverage mHealth and the cloud. Once that obstacle is addressed, artificial intelligence (AI), natural language processing, and machine learning hold great promise.

For example, AI is deeply valuable in detecting safety issues earlier and understanding causes, cross-referencing diverse data sources to understand variables that could be related to a bad drug reaction. For instance, a patient's drug adherence, activity and stress levels, sleep patterns, or diet could be combined with clinical data such as blood pressure or glucose levels. Location information could be cross-referenced with local temperatures, air quality, or allergens present—factors that could prove important in the final analysis. The more complete a picture of the patient, by leveraging mHealth, the more likely AI will be able to generate important insights about factors that might affect how a treatment performs. Additionally, with mHealth, it is no longer a point in time when a patient checks into a labsite; it can be a continuous flow of cross-referenced data.

All this information and insight enables another critical change in clinical trials: making them more patient-centric. Traditionally, clinical trials are one-way affairs, where patients provide valuable data to researchers, but little information flows back to the subject. Now it's possible to provide patients with insights into their own health, recommendations on changes they can make to improve it, and help in managing the condition or disease that led to their selection for the trial in the first place. This same technology can be used later to help individual practitioners become better able to serve their patients through monitoring how well they are following a treatment protocol, or by the biopharma companies themselves as part of the post-trial pharmacovigilance process.

mHealth is an integral piece of the clinical trial operational hub

If there's any hurdle to building this digital future for clinical research, it's not about what the technology can do but how it has been implemented. Many companies have taken an approach over the years that has resulted in siloed systems that make it difficult to link and share clinical data with different parts of the process and different teams involved in the study. Additionally, many clinical trials have been designed around systems purpose-built for a single disease or disease state that are difficult or expensive to use for other types of studies.

What we see happening now in the eClinical space is this movement to a unified eClinical environment that provides an operational hub where all the clinical data is collected—through mHealth and by other means—and analyzed and shared via dashboards and tools that are needed for a specific trial. The goal of this movement is to break down these system-created virtual silos to keep patient data unified in a single place, and provide access to the data by all relevant parties. Rather than force therapeutic teams to wait months or even years for IT to integrate a new sensor or data stream into an in-house platform, the new eClinical environments empower investigators to add new technology easily and quickly to their work, taking advantage of innovation in a timely fashion.

Making these advances practical will depend on a robust and flexible cloud infrastructure that serves as both a repository for the immense amounts of data involved as well as for the tools and intelligence to analyze that information. It also will require changes across life sciences—new roles, standards, and skills will be needed. Regulators will need to adapt legacy processes to accommodate the accelerated pace made possible by mHealth innovation. In addition, privacy and security concerns will have to be addressed in ways that make patients comfortable with providing the data and give enterprises incentives to collaborate.

Ultimately it is about empowering therapeutic teams to embrace new digital approaches that can bring effective life-changing therapies to market, which is the goal we all share.

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Pediatric Oncology Clinical Trials in Sub-Saharan Africa

Peter Wasswa, MD

The region is significantly underrepresented in clinical development activity targeting childhood cancer.

EMERGING MARKETS

Despite contributing to pioneering work in childhood cancer, exemplified by the first description of Burkitt lymphoma nearly 50 years ago,[1] Sub-Saharan Africa (SSA) has since lagged behind. In contrast to cure rates of more than 80% in high-income countries (HICs), in many parts of SSA, less than 20% of children with cancer are cured. With SSA bearing 30% of the global burden of childhood cancer, addressing this disparity in cure rates is critical.[2] Enrollment in high-quality sequential clinical trials that are refining interventions over time has helped drive the success achieved against childhood cancer in HICs. To date, only two active childhood cancer clinical trials from SSA are registered.[3]

The Medline database contains only 13 childhood cancer publications from clinical trials in SSA, of which indigenous SSA senior authorship was less than 20%. Clearly, SSA is underrepresented in pediatric oncology clinical trial activity, and this may have a bearing on dismal childhood cancer outcomes in the region.

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The need for childhood cancer-focused clinical trials in Sub-Saharan Africa

The need to improve outcomes of childhood cancer in SSA calls for the introduction of effective and safe interventions. Robust locally generated evidence does not exist for most cancer treatments in SSA.[2] The evidence obtained from clinical trials conducted in HICs may not be fully generalizable to SSA due to the significant host/patient and healthcare system differences between HICs and SSA.

Host: As a result of poor or delayed access to quality diagnostic services, children in SSA are more likely to be diagnosed at a more advanced stage of disease. There is also a higher prevalence of comorbidities such as malnutrition, HIV, and other tropical infections. Moreover, the ethnic differences between children in HICs and SSA may mean that they are not biologically

comparable to allow generalizability of trial data from HICs to SSA.

Disease: Cancers such as Kaposi sarcoma and endemic Burkitt's lymphoma are unique to SSA, and, therefore, of less interest to clinical research groups based in HICs. As such, researchers and clinicians in SSA must show leadership in developing evidence-based effective cancer interventions through clinical trials.

Health and social care infrastructure: Childhood cancer care provided in HICs is expensive and unaffordable for most countries in SSA. Furthermore, social security support systems for children with cancer are weak in SSA, resulting in increased household poverty and poor treatment compliance. The development of innovative low-cost, low-technology cancer therapies requiring minimal inpatient stay should be prioritized. The role of clinical trials in developing these interventions cannot be overstated.

The challenges of undertaking clinical trials in SSA

Medical researchers face many hurdles throughout the clinical trial process in SSA, including:

Lack of resources: Childhood cancer clinical trials are expensive to conduct and, inherently, unattractive to pharmaceutical companies. With public healthcare resources in SSA stretched to the limit, the scope for conducting clinical studies in SSA is also scarce. This challenge is compounded by a shortage of trained and experienced researchers in the area to perform trials.

Ethical concerns: Compared to HICs, SSA is often considered more "research friendly" because of its less stringent regulatory environment. However, this perceived convenience raises many concerns about the ethics of clinical trials in SSA, given the vulnerability of most research subjects in the region. Vulnerability to coercion may stem from actual or perceived lack of care options for subjects outside study settings. Furthermore, SSA has a shortage of personnel trained to provide ethical oversight through institutional review boards (IRBs), leading to a delay in IRB decisions.

Opportunities clinical trial protocols may deliver to SSA

Although the clinical trial landscape in SSA currently presents many challenges and questions, especially compared to studies performed in HICs, the research community is optimistic about the progress being made in SSA. Particularly in the childhood cancer research community, we expect to see a number of opportunities arise in this region, including:

Supporting clinical care: As has occurred in HICs, clinical trials in SSA could help to inform interventions that ease suffering and improve cure rates for children with cancer in the region. Studies may provide funding for care interventions and human resources in SSA, where competing clinical priorities abound despite constrained national health budgets.

Building research capacity: Clinical trials present a conduit through which the human and infrastructure resources for healthcare and research can be enhanced. Diagnostic equipment and other research project capital purchases often outlive the duration of individual clinical trials. The research and technical skills developed through training and active research participation by SSA staff widens the pool of local research talent.

Building collaborations: The disparity of skills and resources between HICs and SSA calls for healthcare and research partnerships between the two communities. The spectrum of diseases and challenges across SSA is fairly common; therefore, institutions need to work more closely together. For example, the development of research networks that can drive multicenter clinical trials would be beneficial to all parties.

> The evidence obtained from clinical trials conducted in high income countries may not be fully generalizable to Sub-Saharan Africa due to the significant host/patient and healthcare system differences.

Partnership with HICs can enable the transfer and exchange of research skills and mentorship of SSA-based researchers to lead the drive for improved outcomes for children with cancer in SSA. Patients in HICs stand to benefit from multinational clinical trials conducted across sites in SSA and HICs.

Notwithstanding the difficulties, the need for childhood cancer clinical trial activity in SSA to help provide better treatments for kids across the world is self-evident. The unmet need provides a unique opportunity for researchers and institutions in both HIC and low and middle-income countries (LMIC) to collaborate and develop innovative solutions that will positively impact childhood cancer outcomes within SSA and globally.

References

1. Burkitt D. A Tumour Syndrome Affecting Children in Tropical Africa. *Postgraduate Medical Journal*. 1962; 38:71-79
2. Jonas A. de Souza, Bijou Hunt, Fredrick Chite Asirwa, Clement Adebamowo, and Gilberto Lopes Global Health Equity: Cancer Care Outcome Disparities in High, Middle and Low-Income Countries. *Journal of Clinical Oncology*. 2016 34:1, 6-13
3. Gopal S. Cancer trials in sub-Saharan Africa: Aligning research and care. *PLoS Medicine*. 2017;14(7):e1002351. doi:10.1371/journal.pmed.1002351.

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Ensuring High-Quality Data in Complex, In-Home Clinical Trials

To support complex in-home clinical research and investigative sites, well-designed trials must produce the same high-quality data as traditional sites.

Eric Hayashi, MBA
President and CEO,
LabConnect LLC

Patient centricity is an industry obsession—with good reason. It can provide patients easier access to potentially life-changing treatments and can drive scientific progress and generate ROI. In a recent survey, 77% of clinical research stakeholders said it was "very" or "extremely" important that their company embrace patient centricity, and in-home clinical trials offer one of the best opportunities to do so. However, unique challenges in design and execution must be addressed for these trials to yield quality data.

While patients commonly are asked to travel to clinical trial sites in order to participate in research, an in-home trial is a compelling alternative. These trials enable the patient to remain at home, work, or another convenient location, leaving it up to the study coordinator or nurse to travel to them to collect samples and manage monitoring tasks. The benefits to the patient are clear: comfort and convenience, with savings in time and expense. For the research team, benefits include easier patient recruitment, better retention, and better protocol adherence. These are high-value advantages at a time when study subjects are hard to find.

However, in-home studies pose a critical question. Is it realistically possible to get high-quality data from in-home studies with their inherent variability, logistics challenges, and limited oversight? The answer is, yes.

Effectively managing complex in-home studies is critical and becoming more so since the advent of precision medicine. Working with a research organization that has a global laboratory network and sampling logistics is essential. But by also tapping into knowledge gained from companies experienced specifically with in-home clinical research, sponsors will make these complex, in-home trials more manageable while ensuring they provide the high-quality data that clinical research demands.

Supporting complex in-home trials worldwide requires the same streamlined continuity of service and global laboratory capabilities investigational sites always need, with an added layer of organization. Advances such as precision medicine are making protocol adherence, sample logistics and reporting, and collection of high-quality data more complicated. For example, peripheral blood mononuclear cell (PBMC) isolations are gaining importance in clinical trials across numerous therapeutic areas, especially in immunotherapy studies. Samples, once obtained, must be processed quickly by a lab with experienced technicians. In some areas of the world, finding the right lab and getting the samples there in time are nearly impossible without a global network in partnership with an expert in-home clinical trial service provider.

Even more complicated research involving CAR T-cell therapy makes sample logistics and chain of custody more critical than ever. In these complex protocols, the patient is both the beginning and the end of the process, so high-functioning sample logistics is an absolute necessity.

To support complex in-home clinical research and investigative sites, well-designed trials must produce the same high-quality data as traditional sites. New processes and tools must accommodate variability in home sites and caregivers by facilitating sample collection and reporting. For example, clinical kits specifically for home use may include complete supplies for sample collection and shipping with precise instructions for the home health nurse to follow. Other solutions could include simplified methods of reporting for home visits and client informational materials to educate all stakeholders.

Most importantly, logistical expertise and robust systems are required to ensure samples arrive at specialized labs for testing or processing and, for complex trials, that the samples are then returned efficiently and reliably to the patient, with chain of custody intact. In these ways, in-home clinical trials can ensure the data integrity the industry needs while also providing the convenience to improve patient participation and retention.

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