2020: The Industry’s Future Awaits

When you read this, it should be about 50 days until 2020. Here are two stats pulled out of 2017 regarding the drug development enterprise for 2020. It is estimated that the majority (72%) of clinical trials will be run by CROs in 2020, and the internal rate of return (IRR) on pharma R&D is predicted to be at 0% in 2020. Since CROs don’t run clinical trials out of the graciousness of their hearts, there looks to be a bit of unsustainability in the market. What future awaits the industry remains to be seen; here are some more uplifting tidbits around innovation that could help change this bleak prospect.

Exhibit A. Veeva Systems’ 2019 Unified Clinical Operations Survey: Annual CRO Report came out at the end of October (see https://bit.ly/36lDFo4) with these highlights. CROs are initiating change to simplify information exchange with study partners, which they expect to yield significant benefits, including reduction in manual processes (77%), streamlined collaboration (65%), improved study quality (64%), and faster study execution (64%). In addition, the survey found site contracting and budgeting the most cited and fastest growing issue during the study start-up process, with 70% saying it is their top challenge, up 11 percentage points since 2018 and among the primary drivers for change.

Exhibit B. I will be attending Knect 365’s Clinical Trials Europe event this month. Speakers provided their own predictions for the future of clinical trials here: https://bit.ly/34iY2Aa, and I look forward to learning more about the relationship between CROs and sponsors. As stated by Patricia Moenaert, director, portfolio sourcing and relationship management (PSRM) at Celgene, “Sourcing/outourcing will be supported by more automated systems by 2020 and sponsors will mainly do oversight and less micromanagement since both CROs and sponsors will join the same most common technology. This will allow sponsors to be more efficient in resourcing internally and avoid duplication of task by both CRO and sponsor. Non-core activities will be delegated to CROs who are becoming the experts, while study sponsors will stay core at the sponsor.”

Exhibit C. It’s becoming increasingly disingenuous for industry to point fingers at FDA as the block to furthering innovation in drug development. While agency guidelines are paramount to following regulatory intent, even when the guidances literally tell industry they can get away from archaic practices, something keeps the CROs and sponsors entrenched. Former FDA Commissioner Scott Gottlieb had been direct in his comments during his tenure around sponsors and CROs that resist change, noting that there needs to be a more concerted effort by leadership across the entire community to lead that change. He did acknowledge that drugmakers need additional contact or reassurance from FDA, that if they are implementing change, they’re going down the right path. But he believes that FDA’s processes are transparent, and often go through a notice and comment period, either rule-making or guidance. And with recent CDER and CBER restructures and a push for the necessary digital transformation, the regulatory future for innovation is bright. The December issue of Applied Clinical Trials will highlight Regulatory Updates and include articles around FDA pilots, regulatory information systems, and updated information around China, the EU, and more.
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Exploring the nation’s opportunities for growth and the initiatives undertaken to build an attractive clinical trials ecosystem for early stage research.

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Emile Youssef, MD, PhD

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WASHINGTON REPORT

SPONSORS STRUGGLE WITH TRIAL DISCLOSURE, PATIENT PRIVACY REQUIREMENTS

More comprehensive policies for registering clinical studies in the U.S., Europe, and other regions aim to expand access to research data and to provide timely information for patients on promising, new treatments. Wider sharing of clinical trial data and publication of study results is now considered central to ensuring maximum benefit from clinical research programs and for encouraging individuals to participate in the biomedical research enterprise. Such efforts, though, raise potential conflicts with broader privacy requirements, particularly in the European Union (EU) where policymakers continue to widen rules designed to protect consumers from unauthorized disclosure of personal information.

The tension between data disclosure and individual privacy has gained attention as the EU readies full implementation of its General Data Protection Regulations (GDPR), which aims to provide individuals with more control over uses of personal data. Unfortunately, this policy designed to limit unwanted individual exposure via electronic information systems appears at odds with efforts in many regions to promote data transparency policies designed to make biomedical research results more available to healthcare entities and the research community. Key issues are how regulators define “personal data,” whether anonymization can permit flexibility in data use; which parties (sponsors, data processors, third-party researchers) may access data; and to what extent an individual may control uses of their personal data.

In addition, initiatives to establish platform studies that involve multiple sponsors and products, often using common controls, raise additional complexities for data tracking, analysis, disclosure, and privacy protection. And challenges arise from efforts by sponsors to protect confidential business information from release and to reduce the risk of individual re-identification.

Further complexity arises, moreover, as multiple regulatory authorities address these issues, noted research authorities at the Global Clinical Trial Disclosure & Data Transparency conference sponsored by DIA in September. Health Canada, for example, is implementing a revised process for public release of clinical information similar—but not the same—as EU Policy 0070, which requires disclosure of clinical trial results in the form of summary or aggregate data. Separately, the European Medicines Agency (EMA) and Health Canada now are releasing clinical study reports filed to support market applications for new drugs, a transparency issue controversial in the U.S. FDA policies and the Common Rule governing U.S.-funded and regulated biomedical research, however, require the registration of human subject research activities and publication of summaries of study results.

Such efforts to expand access to research information raise concerns for how they will relate to the GDPR and other privacy requirements. This will become more challenging if EU authorities further grant individuals the right to remove personal data from documents and to withdraw consent. A serious threat is that such policies may hinder the transfer of personal data from the EU to U.S. entities, which could limit collaboration between U.S. and EU sponsors and researchers.

Expanding disclosure

Meanwhile, the U.S. system for public registration of clinical trials and disclosure of study results continues to expand. The ClinicalTrials.gov registration system operated by the National Library of Medicine over the past 20 years now lists 300,000 trials plus results from 38,000 studies. This has created “a really rich data resource,” with increased inclusion of full-study protocols, statistical analysis plans, and informed consent forms, commented ClinicalTrials.gov acting director Rebecca Williams at the DIA conference. The program is expected to become even more robust with efforts by the National Institutes of Health (NIH) to clarify requirements for the disclosure and dissemination of clinical trial information for all NIH-funded research.

To ensure that ClinicalTrials.gov continues to provide a valuable resource, Williams is seeking more input from the public and from the full range of users to better understand the needs of parties accessing clinical research information. One issue is whether sponsors should provide narrative or “plain language” summaries of studies that may be more useful for patients and other stakeholders.

The value and the risks of broader sharing of clinical data will be further explored at a public workshop this month sponsored by the National Academies of Sciences, Engineering, and Medicine (NASEM). Experts will examine advances in this area and continuing challenges since publication in 2015 of an Institute of Medicine report on Sharing Clinical Trial Data. A previous meeting in September discussed how more consistent and clearer reporting policies and guidelines could help increase transparency in biomedical research by researchers, institutions, funders, and medical journals.

The November 18-19 session plans to take a broad look at the successes and failures in data sharing and reuse by public and private researchers, as well as perspectives of trial participants, patient organizations, and sponsors. One aim is to reach agreement on ways to better harmonize policies, standards, and incentives to overcome barriers and increase the value of clinical research.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

10/9/19: Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry

10/18/19: Drug Master Files Guidance for Industry (draft)
WHO’S GOING TO BE DISRUPTED BY SHIFTS IN EUROPEAN HEALTH STRATEGY?

In a quiet, offseason week in a remote Austrian ski resort, hundreds of European health professionals and policymakers gathered with the express intention of promoting what is now fashionably called “disruptive” change in European health systems. There could be implications for everyone in the health sector—including everyone involved in clinical trials.

The heady aspirations were spelled out by some of the leading policymakers as the meeting got underway at the start of October, with the main focus on transforming health systems so as to achieve greater equity and sustainability in citizens’ health experience. The tone was set by Piroska Ostlin, who is acting at present as the World Health Organization’s regional director for Europe, increased average life expectancy and levels of health across Europe, “obscure gaps between the most and least advantaged socio-economic groups,” she said. In her view, tackling health inequities requires policies spanning government sectors. And going that way, “would accelerate progress towards inclusive growth and sustainable economic development.”

Outgoing EU Health Commissioner Vytenis Andriukaitis—he left office Nov. 1—reiterated the call he made when he took up the job five years ago: instead of health being governed in separate silos of responsibility, the challenges should be met in a comprehensive manner—covering the environmental, commercial, economic, behavioral, and social determinants of health. “It is time,” he said, “to make a reality of that other fashionable slogan, ‘health in all policies.’”

Ella Mäkipää, Finland’s deputy health minister, invoked the theme of the current Finnish presidency of the EU to, “improve EU decision-makers’ understanding that wellbeing policy and economic policy should go hand-in-hand and that investing in wellbeing enhances productivity and generates economic growth.”

Slovenia’s Minister of Health Aleš Šabeder, wants equity in health, “not only as a value but also a fact,” and makes the case that, “investments in the health system, including in preventive services and in reducing health inequalities, contribute to growth, sustainable development, and societal well-being.”

Christopher Fearne, Malta’s deputy prime minister—and also its longstanding minister of health—said it is time to, “overcome political inertia and push for implementation of policies, even if it means disrupting certain health harming industries”—without specifying which those were. He said it was vital to protect and support those who are falling behind in today’s society and carrying the large proportion of disease burden.” But despite the evident industry-skepticism behind his remarks, he also indicated that he was ready to “work with healthcare providers, professionals, and healthcare industries to embrace the opportunities offered through technology in order to transform our health services.”

The potential of new technologies is another of the themes underlying policymakers’ concerns. “Digitization is indispensable for healthcare transformation,” said Brigitte Zarfl, minister of health in Austria.” But, she added, it must be “fully patient-focused.”

Tanel Kilk, Estonia’s minister of social affairs, shared much of that enthusiasm. “Healthcare must undergo a data-driven transformation to become more personal and sustainable,” she said. In her view, “we need to better harness health data to advance healthcare delivery, health policy, research, and innovation.” And she foresaw cooperation with researchers and industry as an indispensable element in advancing “the good of all Europeans.”

Skeptics may legitimately point out that these are not the major figures on the European stage—they are from mid-sized or small countries, and they are speaking very much off-stage rather than on the main European stage. But similar sentiments are being heard with increasing frequency and volume in Italy, Spain, France, and the UK. And this is, as this meeting in Gastein underlined, “a time of new beginnings for Europe, with a new European Parliament installed, the next mandate of the European Commission kicking off [this month], and the election of a new regional director for WHO Europe.”

For the research community and developers of healthcare products, the suggested shift in emphasis in healthcare strategy could reduce the attention—and funding—to therapy, or might subject research funding to tighter controls over the suitability of research projects for the new agenda. It might equally well impose tougher limits on the provision of healthcare that fails to meet preordained objectives. Or, again, it might mean a big boost for all aspects of innovative healthcare. Whichever way the trend goes, it is certainly one to keep watching.

— Peter O’Donnell

DEFINING THERAPEUTIC INDICATIONS

The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has developed a document to increase consistency when defining therapeutic indications in the product information of medicines.

The paper is intended to guide assessors in the national competent authorities who are responsible for evaluating marketing authorization and extension of indication applications received by EMA. It outlines key elements to consider when evaluating the indications proposed by the applicant, for example, whether a medicine is considered as first- or second-line treatment or should be used in combination with another product.

CHMP’s paper takes into account some of the needs of healthcare decision-makers such as healthcare professionals and health technology assessment (HTA) bodies.

— Peter O’Donnell
THE ‘QUEST’ FOR AN EFFECTIVE PARTNER IN PHARMA AND BIOTECH

Quest Diagnostics has built a series of collaborations with data providers that enable clients to link data sets with matched, de-identified data in order to understand the clinical trial patient journey. In this interview, David Freeman, general manager, Information Ventures, for Quest Diagnostics, discusses how the company uses its laboratory data to try to be an effective partner for pharmaceutical and biotechnology companies.

Q: Can you briefly describe Quest’s Clinical Insights and Clinical Trials Connect products, and how long they took from concept to product? Can you describe how each works in practice?

David Freeman: Most people I talk to in pharma and biotech know that Quest Diagnostics is a leader in laboratory diagnostic services. What they often don’t know is the depth of our experience and capabilities in data, analytics, and services across the development continuum. Beyond having over 48 billion clinical lab results in its database, Quest has 2,250 patient service centers, increasingly in retail locations, 20,000 mobile care professionals seeing patients in workplaces and the home. Quest provides services to half the country’s hospitals and physicians, roughly a third of the adult U.S. population every year.

The Clinical Insights portfolio started in 2015 with dialogue between Quest data scientists and medical directors with researchers in pharma who were trying to understand large patterns in disease progression, diagnosis, and treatment. Those dialogues, which continue to this day, produce rich insights and customized at-scale data sets and analysis used for research and the planning of new therapeutic launches.

As our clients have realized how powerful clinical laboratory insights can be, they have asked us to enhance our offering in two important ways. The first centers around enabling the linkage between diagnostic laboratory insights with other data sets, and the second is to add services linked to patient recruitment in clinical trials. Recruitment offerings typically start with the sponsor or CRO sharing the inclusion and exclusion (I/E) criteria for a study. We use those criteria to provide three core services:

1. Site and investigator identification and validation—based on the I/E criteria, do the clinical trial sites and investigators have an active patient pool that matches the study?
2. Physician outreach—to identify either potential principal investigators (those with 1572s filed) or physician referral networks, based on Quest relationships.
3. Patient outreach—Quest has an identified patient relationship and can outreach to patients to inquire if they are interested in learning about clinical trials opportunities. Taken together, the Clinical Insights and Trials Connect capabilities support assessment, planning, and outreach in therapy development, from research all the way through to commercial launch.

Q: How much data cleaning, API building, or other tech involvement is required?

DF: Quest has been systematically investing in our data capabilities, connectivity, and partnerships for years. For example, Quest works with half of the country’s hospitals and physicians. To enable those relationships, Quest has over 650 active EMR (electronic medical record) interfaces that enable ubiquitous test ordering and high-availability results reporting.

For our pharma and public health customers, many of them have invested in clinical data sets that are particularly relevant to their disease focus. Quest has built a series of collaborations with data providers that enable these clients to link those data sets with matched, de-identified data in order to understand the patient journey, patterns in disease progression, acuity stratification, etc. For example, a therapy company may have a cardiovascular pipeline and has invested in an events database that contains stroke and heart attack data. Quest can leverage its laboratory data to perform analysis to match relevant biomarkers so that intervention opportunities and linkages between labs, medication history, claims and outcomes could be explored. Quest has invested in multiple de-ID collaborators so that our clients can choose from one of the six de-identified output formats, based on which “dataverse” they have previously invested in. A core principal for our data, analytics, and services business is that we do not lock our customers into only one data format or CRO.

Q: How does the physician get notified that a patient is a potential fit for a clinical trial?

DF: Quest Diagnostics is in a position of being able to contact a physician who may serve patients that are suitable for a trial. This contact may occur through one of our medical directors, for instance, and if the clinician is interested, more information is provided.

Effective patient recruitment has been a huge challenge for drug development. For every 100 patients that express interest in participating in a trial, 69% of those patients fail the pre-screen. That screen-failure rate is expensive, time-consuming, and frustrating to the site team and patients. Starting with known patients and matching their health history against study inclusion/exclusion criteria is a critical step in addressing this issue.
THE GROWING IMPORTANCE OF REAL-TIME ACCESS TO CLINICAL STUDY PERFORMANCE

To paraphrase the 16th century English poet John Donne, in today’s global life sciences arena, no company is an island. Clinical trial sponsors rely on contract research organizations (CROs), clinical service organizations (CSOs), and technology providers to augment their capabilities in the conduct of clinical trials—and in some cases for total study conduct. Indeed, CRO-conducted clinical research increased 40% from 2008-2014, and by 2022 is projected to top $45 billion per year. Conversely, the raison d’etre of these organizations is to service the biopharma community. As a result, in this unique, dynamic 21st century clinical development ecosystem, all organizations supporting or involved in the conduct of clinical trials must be able to share data and provide study updates in real time. These updates are critical so clinical operations teams can, in real time, see how trial enrollment is progressing, understand where areas of risk or concern exist, and be empowered to take immediate corrective action.

The power conferred by such real-time intelligence directly impacts the efficiency, cost, and reliability of clinical operations, ultimately enabling sponsors and CROs to bring important new therapies to market both cheaper and faster. Within the clinical development ecosystem, sponsors and their partners need data analytics platforms that provide a single source of truth about large, disparate data sets, so they can assimilate and exchange clinical trial information in an integrated way for actionable views at any point in time. Harnessing and truly optimizing the full power of clinical data for improved insights and better decision-making is the ultimate competitive advantage in an industry strictly governed by safety, efficacy, and regulatory guidelines, and for which time and cost factors are so critical. Having invested an estimated $90 billion in R&D activities in 2016 alone, biopharma regularly spends an average of six times more on R&D as a percentage of sales than all other manufacturing industries.

Unfortunately, there are limited number of data analytics systems suited to provide such sophisticated and immediate insights for companies whose data is spread far and wide across different business entities, applications systems, databases, and geographies. The optimal data-driven clinical development decision-making process, which is attainable with the right analytics solution, should be swift, clear, and error-free. The reality, however, is that most companies in today’s clinical development ecosystem are either not employing such a system or using suboptimal systems, and, therefore, their decision-making paradigm is cumbersome, risky, and error-prone. Most stakeholders, unfortunately, spend more time wrangling their data, to inefficient results, than using data-driven insights to optimally manage their trials and portfolios.

Whether clinical trial data is being examined by a sponsor or CRO, a portfolio lead, or study manager, the name of the game is direct line-of-sight and real-time access to study status. Legacy data platforms are no longer enough for the clinical trials, the most time- and resource-intensive phase of drug development. The need to see real-time study performance is imperative, as project teams focus on meeting timelines and ensuring resources are appropriately allocated. Machine learning-based analytics solutions provide instantaneous views of an organization’s data and can be leveraged across multiple portfolios by sponsors and across multiple sponsors by CROs. When sophisticated, qualified data analytics platforms are properly activated and implemented, problems are solved, obstacles are overcome, costs are reduced, and therapeutic development is accelerated to bring needed drugs to market faster than ever before.

Q&A

Q: As industry moves into very specific targeted therapies, how do you see your services evolving?

DF: Today’s therapeutic landscape is very different than it was 20 years ago. Precision medicine, where new therapies are targeted to a patient’s specific genotype and phenotype, in essence, means that every new drug is a rare disease drug. This had led to amazing new therapeutic breakthroughs that also carry added complexity from a patient recruitment perspective.

With the largest diagnostic testing compendium and advanced companion diagnostics capability, Quest is extremely well positioned for the long run as an effective partner for pharma and biotech firms.

Q: What are your plans for further development and collaborations?

DF: There is a lot of innovation occurring in the clinical trials ecosystem and we are extremely proud to be part of that. Quest has a number of important partnerships and will continue to expand those in order to extend the range and value of our services.

References
2. https://www.phrma.org/advocacy/research-development

— Jonathan Zung, PhD, is Executive Vice President at WCG and a member of the Saama Technologies Clinical Board of Advisors
EUROPE RECRUITING ADDITIONAL TEAMS FOR SPECIALIZED RARE DISEASE NETWORKS

There’s less than a month left to join Europe’s networks of expertise for rare and complex diseases, the European Reference Networks. Until Nov. 30, hospital-based specialists can apply to become members of one of the 24 European Reference Networks (ERNs) that the European Union launched in 2017, and that now include 956 healthcare units from 313 hospitals located in 26 countries. They cover a wide range, from bone disorders and pediatric cancers to endocrine conditions, and from epilepsies and congenital malformations to kidney diseases.

Created under the EU’s 2011 directive on cross-border healthcare, these networks bring together centers of expertise and reference centers of European hospitals to tackle rare or low-prevalence diseases and other complex conditions that require highly specialized healthcare. The aim is to allow specialists in Europe to share their experience with complex patient cases, and to provide advice on diagnosis and treatment. To review individual cases, ERNs convene “virtual” advisory panels of medical specialists across different disciplines, using a dedicated IT platform and telemedicine tools. The underlying principle is that the knowledge travels, rather than the patient, with the intention of leading to economies of scale and more efficient use of costly resources.

The concept emerged from the challenge that knowledge and resources on specific rare conditions are scattered across Europe’s individual countries, none of which, operating alone, have the capacity to treat all rare and complex conditions. The EU’s networks help to connect the dots, maximizing expertise by cooperating and exchanging knowledge at the European level, and giving patients across the EU access to the best expertise available.

It is a peculiarly European response to a peculiarly European problem—a multiplicity of small countries (even Germany, by far the biggest, has only 80 million inhabitants) with distinct healthcare systems and research infrastructures that suffer from a chronic lack of coordination or even communication with one another across the continent’s internal national frontiers. Add to that the specific challenges of tackling rare diseases; as many as 8,000 rare diseases affect the daily lives of around 30 million people in the EU, in oncology alone, there are almost 300 different types of rare cancers and each year more than half a million people in Europe are diagnosed with one of them.

But many affected by a rare or complex disease have no access to diagnosis and high-quality treatment: where patient numbers are low, expertise and specialist knowledge are often scarce.

The membership application process can look daunting, since a healthcare team has to get endorsement from the head of its hospital and from its national health authority, and candidates are then screened by a board of representatives from the participating health authorities. But the benefits extend beyond the chance for taking part in reviews of complex cases. They include the opportunity to play a role in the development of guidelines and in training, and to join large clinical studies aimed at improving understanding of rare diseases. The patient data gathered also contributes to the development of new drugs and medical devices, and ERNs are influential in the emergence of new care models, and e-health solutions and tools.

At a time when Europe is facing a string of new tensions—ranging from internal disputes over migration, budgets or carbon-reduction targets (to say nothing of Brexit) to external challenges such as threats to the multilateral trading system, growing disorder in the Middle East, and the shifting power balance between the U.S., Russia and China—this local but effective initiative is a welcomed demonstration of how cooperation can function in the common interest.

— Peter O’Donnell

NEW FDA MODEL AIMS TO SPEED MORE RARE DISEASE TREATMENTS

The development of new therapies to treat orphan diseases is particularly perilous, due to limited patient populations, high costs, and difficulty in measuring clinical effectiveness. FDA officials are addressing these issues through the Rare Disease Cures Accelerator (RDCA) initiative in the Center for Drug Evaluation and Research (CDER). The goal is to shift away from a system of fragmentary research methods plagued by poor quality evidence to a more coordinated research approach and methods that can expedite development of drugs to treat rare diseases.

Main strategies involve establishing common platforms and standardized tools and infrastructure to improve the quality of clinical trial data, explained Theresa Mullin, CDER acting director for strategic initiatives, at the Rare Summit sponsored by the National Organization for Rare Disorders (NORD) in Washington, D.C. last month. Mullin described how a more cooperative and collaborative approach can improve the quality of study endpoints, promote trial designs that accelerate learning, reduce missteps that cause failures and delays, and generate evidence needed for regulatory approval.

The RDCA provides the infrastructure for a cooperative approach to designing and conducting clinical trials in rare diseases to improve testing, protocols, and patient enrollment in clinical trials, Mullin noted. FDA is collaborating with the Critical Path Institute, NORD, patient groups, industry, and other stakeholders on a framework for conducting more standardized rare disease natural history studies to help target treatment and design appropriate trials. This involves examining the underlying causes of a disease, how it changes over time, variables in symptoms and experiences, and how the disease differs across populations. Patient perspectives remain key to providing insight into the most important impacts and what constitutes ”meaningful change” in symptoms.

— Jill Wechsler
STUDY WILL ASSESS THE EFFECTIVENESS OF STATINS IN OLDER ADULTS

A $90 million award expected from the National Institute of Aging and the National Heart, Lung, and Blood Institute (NHLBI) will fund the largest pragmatic trial with placebo-controlled drug assignment to date. Building on its success in leading pragmatic approaches for clinical study design, the Duke Clinical Research Institute (DCRI) has been awarded funding to conduct a pragmatic trial studying the effectiveness of statins in older adults without known cardiovascular disease. Funding for the trial is expected to be spread over the next seven years.

The study, known as Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE), will be funded by NHLBI, of the National Institutes of Health (NIH), and conducted in partnership with Wake Forest School of Medicine. PREVENTABLE also is the first statin trial with a non-cardiovascular primary outcome. Investigators will study whether statins could help prevent dementia or physical disability—the most important outcome for older adults looking to maintain independence. Few statin studies in primary prevention populations have included individuals aged 75 or older, leaving many unanswered questions for older adults.

PREVENTABLE will partner with PCOR-net, the National Patient-Centered Clinical Research Network, and the National VA Network to identify and recruit 20,000 participants 75 years of age or older at 100 U.S. sites, as well as to help identify outcomes via electronic health records. Use of these two national resources is expected to enable investigators to enroll participants and collect health data faster and more efficiently than a traditional trial.

Medidata acquisition closes

The acquisition of Medidata Solutions, Inc. by Dassault Systèmes SE was completed late last month. Medidata offers clinical expertise and cloud-based solutions supporting the development and commercialization of treatments.

The acquisition positions Dassault Systèmes to be a key player in the digital transformation of life sciences in the age of personalized medicine and patient-centric experience through a comprehensive offering that reflects a deep understanding of healthcare, its ecosystem, and market needs. Medidata will operate as a Dassault Systèmes brand powered by the 3DEXPERIENCE platform. The life sciences industry will become Dassault Systèmes’ second-largest core business after transportation and mobility.

Under the terms of the agreement, first announced in June, Dassault Systèmes acquired all of the issued and outstanding common shares of Medidata for $92.25 per share in cash, representing a total enterprise value of approximately $5.8 billion.

Astellas and Pandion strike pact

Pandion Therapeutics, Inc. and Astellas Pharma, Inc. signed a license and collaboration agreement directed toward the research, development, and commercialization of locally acting immunomodulators for autoimmune diseases of the pancreas. The collaboration will allow the parties to combine Pandion’s modular biologics and functional immunology expertise with Astellas’ advanced therapeutics development and global commercialization capabilities for the treatment of autoimmune diseases.

Under the terms of the deal, Pandion will be responsible for design and discovery of bispecific drug candidates based on Pandion’s proprietary modular immune effector and tissue tether platform and Astellas will be responsible for conducting preclinical, clinical, and commercialization activities for the selected candidates developed during the collaboration.

Parexel expands SCRS collaboration

Parexel announced the expansion of its collaboration with the Society for Clinical Research Sites (SCRS), the first and only global organization fully dedicated to representing the interests of clinical research sites. Parexel will participate as a Site Engagement Partner and lead a number of key initiatives focused on improving the patient experience in clinical trials. The company’s global site solutions team maintains a site alliance network of more than 500 sites and 17,100 investigators across the globe.

One initiative Parexel will work on with SCRS will be leading a site advocacy group (SAG) on diminishing patient burden in clinical trials, bringing sites and patients together to discuss patient perceptions of methods of reduction of patient encumbrance to participate in clinical trials.

CF ‘Path to a Cure’ launched

The Cystic Fibrosis Foundation unveiled its “Path to a Cure” last month, an ambitious research agenda to deliver treatments for the underlying cause of the disease and a cure for every person with cystic fibrosis (CF). The Foundation is challenging potential collaborators to submit proposals that will accelerate the pace of progress in CF drug discovery and development and intends to allocate $500 million to the effort through 2025.

The Foundation offers partners a range of resources to de-risk CF drug discovery and development, including the world’s largest network of CF clinical trial sites and a dedicated laboratory to support translational research for potential therapeutic programs.

First Ebola vaccine inches closer

The European Medicines Agency (EMA) announced its conditional marketing authorization of a vaccine used to prevent the spread of the Ebola virus. University of Florida researchers played an integral role in the design and analysis of trials testing the effectiveness of the vaccine, manufactured by Merck & Co. Conditional authorization brings the vaccine a major step closer to licensing, which will eventually make the vaccine more widely available to protect people who are at risk of contracting Ebola.

Alexion to purchase Achillion

Alexion Pharmaceuticals, Inc. and Achillion Pharmaceuticals, Inc. have entered into a definitive agreement for Alexion to acquire Achillion, a clinical-stage biopharma company focused on the development of oral small molecule factor D inhibitors to treat people with complement alternative pathway-mediated rare diseases, such as paroxysmal nocturnal hemoglobinuria (PNH) and C3 glomerulopathy (C3G).

— Staff and wire reports
Establishing Early Phase Capabilities in Malaysia

AJA Ooi, KF Khalid

Exploring the nation’s opportunities for growth and the initiatives undertaken to build an attractive clinical trials ecosystem for early stage research.

Industry-sponsored research (ISR) has been progressively growing within Asia in the last decade. Early phase clinical trials play a crucial role not only in drug development, but also in expanding the clinical trial ecosystem, bringing in scientific knowledge and novel medical technologies and treatments to individual countries. The benefits of conducting early phase trials also extend towards a "spillover" effect of boosting locally conducted later phase trials, leading to access of novel treatments by a large and relatively naïve patient pool and bringing in investments.

With over 20 years experience in conducting late-phase clinical trials, the Malaysian government realizes the positive impact of encouraging the growth of early phase clinical trials. The country also has an untapped potential that can be used toward delivering high quality early phase clinical trials, such as a naïve and diverse patient pool, established and experienced infrastructure, capabilities and resources, and competitive regulatory timelines compared to its neighboring countries.

In view of this, there is a strong focus on growing the clinical trial ecosystem in the country by optimizing the already existing resources while expanding and improving them to further facilitate early phase ISRs in the Malaysia. Clinical Research Malaysia (CRM), established for this purpose in 2012, and a Phase 1 Realization Project (P1RP) was launched in 2016. Supported by five pillars ranging from development of guidelines to people and capability development, the goal is to enable Malaysia to cater to early phase drug studies.

Growing appeal
The conduct of ISR in Asia has been gaining momentum for more than a decade. A 2017 Frost & Sullivan white paper states that the contract research organization (CRO) market in Asia-Pacific (APAC) is the fastest-growing in the world with an expected compound annual growth rate (CAGR) of 20% (from 2016-2021) compared to an increase of 11.4% CAGR globally. This follows from estimates of clinical trial volumes increasing from 5.9% of the total global volume between 2005-2007, to 9.7% in 2011 in the APAC region, showing a steady influx of clinical studies, as it gains a reputation for being a preferred destination for ISRs.

However, a lack of early phase trials (Phase 0 and I studies) is evident. Louisa et al. examined the number of ISR Phase I trials between 2007–2009 and found that only 6.8% of them made their way to the APAC region. The early phase clinical trial market in 2013 was valued at approximately $11.9 billion USD with an expected CAGR of 1.5–2%, reaching 4% this year. Owing to the important roles of early phase trials that range from their scientific benefits to capacity-building and economic advantages, most Asian countries, including Malaysia, have focused initiatives into building adequate infrastructure to attract them.

Early phase trials: Asian benefits
As of last summer, there were 16,248 interventional ISRs covering all phases globally; 27.2% (4,424) were in the early phases (Phase 0 and I trials). Figures 1 and 2 (see page 12) show the proportion of early phase trials in Asia and Southeast Asia, which are significantly smaller levels compared to North America and Europe.

There are several benefits in conducting early phase trials in Asia. One is that there are certain diseases that are more prevalent in Asia compared to the West, wherein epidemiology, health services, social determinants, comorbidities, and genetic components of the population can influence how a treatment may be
A record number of new oncology drugs have been approved in recent years, bringing new treatment options to patients. However, despite robust levels of pipeline activity, oncology trials are complex and remain a challenging area for research and development.

Join this webinar to learn about trends shaping the development and delivery of cancer treatment worldwide. We will share insights and best practices to help ensure your future oncology trials are designed to be quick and efficient and yield high-quality data for the best chance of success. Our experts will address specific considerations for biotech companies embarking on oncology trials.

Key take-aways:

- Understand top trends driving change in oncology clinical development today and through 2023.
- Recognize the impact of new therapies and care standards on trial planning and design.
- Learn how to apply real-world evidence to trial design, trial start-up, and trial conduct for more efficient and effective trials.
used, as well as differences in genetics and gastrointestinal microbiome effect on the pharmacokinetics and pharmacodynamics of drug molecules. There have also been concerns that racial and ethnic minorities, women, and the elderly are often underrepresented in early drug development programs, making Asia an attractive destination for clinical trials.

The conduct of more early phase trials in regions within Asia, like Southeast Asia, can play a pivotal role in ensuring that the populations proportional to the potential uses of the product after its registration and approval are performed from the earliest stages.

**Early phase trials: Opportunities for growth in Malaysia**

**Diverse and accessible subject pool**

Malaysia, located in Southeast Asia, is a multi-racial country consisting of Malays, Chinese, Indians, and numerous indigenous people who are mostly treatment naïve. This provides the genetic diversity that is important in every clinical trial. The epidemiology of diseases in an individual country is also a crucial consideration when determining the success of a clinical trial, as it signifies the availability of study subjects and mitigates the risks of poor accrual rates that can cause trials to fail at huge costs. Though a strong presence of the disease targeted provides for a rich source of ready patients for later phase clinical trials, it also serves as an important incentive for governments to encourage testing of novel treatments in first-in-human (FIH) trials within the country.

**Patient pool with cardiovascular risks—diabetes, hypertension, hypercholesterolemia**

At a global level, the top 20 indications of ISR trials, regardless of phase of study, include cardiovascular disease, diabetes mellitus, hypertension, and hypercholesterolemia. Conducting early phase trials targeting these conditions would be doubly beneficial to countries like Malaysia that face major public health concerns with them. Early phase trials would allow access to novel treatments and changing standards of care, and with a ready pool of relatively naïve patients, sponsors and CROs would have easy access to subjects for later phase trials. Being part of the drug development process from its early stages allows investigators and clinical trial staff to become familiar with the treatment, thereby allowing continued progress of clinical study phases to occur more smoothly.

In Malaysia, the National Health and Morbidity Survey, published in 2015, showed that prevalence of diabetes mellitus among Malaysian adults 18 years old and above was 17.5% (8.3% known and 9.2% undiagnosed). The overall prevalence for hypertension and hypercholesterolemia was 30.3% (13.1% known and 17.2% undiagnosed) and 47.7% (9.1% known and 38.6% undiagnosed), respectively.

In 2016, disease of the circulatory system was among the top five principal causes of hospital admissions (both private and public hospitals), at 7.44% of total admissions, and was among the top five principal causes of death in Malaysia.
mortality.11 With regard to type 2 diabetes mellitus, diagnosis of disease in Malaysia has more than doubled since 1996, and coupled with an overweight and obesity prevalence of 27–31% in school children, the condition poses a major public health concern.11

With the high prevalence of cardiovascular risk factors such as diabetes, hypertension, and hypercholesterolemia, not only has Malaysia a ready, diverse, and relatively naive patient pool for later phase ISRs that fit into the top 20 clinical trial indications, but it also gives the Malaysian government a strong incentive to encourage early phase trials.

Oncology patient pool

Studies in the field of oncology treatment are currently the top indication for clinical trials. Using the following search criteria, start date 01/01/2013-12/31/2017, recruiting, not yet recruiting, active—not recruiting, enrolling by invitation, early Phase I and phases I-III, indications for cancer takes up 54.5% of the total industry sponsored interventional studies.10 Additionally, projected distributions of available new active substances in the global market by disease type from 1996–2020 show a projected growth in oncology biopharmaceuticals and pharmaceutical products making up 13% of the total new active substances.20 Thirty-three percent of novel drug approvals in 2015 by FDA were for oncology-related products, while 27% were approved in 2017.16 In the U.S. alone, there were 836 drugs and vaccines for cancer in various stages of clinical development or awaiting FDA approvals.19

In Malaysia, cancer is within the top five causes of mortality, and in 2016, the total hospital admissions for neoplasms were 4.2% (based on total admissions of > 3 million).10 Breast cancer is the most common of all cancers (17.7%), followed by colorectal (13.2%) and cancer of the trachea, bronchus, and lung (10.2%).20

FIH oncology trials differ from early phase trials in other therapeutic areas—they are evaluated in patients rather than healthy volunteers. The characteristics of oncology products, mainly their safety profiles, do not allow for testing in healthy volunteers. In the absence of alternative effective treatments, participation in these trials using novel compounds are considered an opportunity to these patients.21 Therefore, with the global pipeline of oncology drugs in clinical development having seen robust growth over the past two decades,22 combined with the strong presence of cancer among Malaysians, not only are sponsors presented an opportunity to tap into the available pool of cancer patients, it is also a considerable push for the Malaysian government to spur the growth of early phase oncology clinical trials within the country.

Cost effectiveness

The cost of developing a new molecular entity can be over $1 billion USD with an average estimate of $2.6 billion USD.6 Added to that, the development of a new medicine from identification through approval for marketing can take up to or more than 12 years. In view of the extreme financial investments, Asian countries like Malaysia, which provide treatments and medical procedures at a lower cost than in developed countries,10 can be seen by sponsors and CROs as an ideal site for conducting clinical trials with lower investments.

The 2017 Frost & Sullivan white paper’s costing estimates of conducting clinical research per patient, per visit, in all therapeutic areas and in all phases, shows Malaysia as having the second-lowest cost, ahead of India ($350 vs. $330 USD); while costs in Singapore was similar to that in the U.S. ($1,210 vs. $1,380 USD) and that in South Korea ($890 USD).

Regulatory timelines

One of the complexities of performing clinical trials in Asia is the heterogeneous nature of the regulatory processes and timelines among the countries in the region.1,2,6

However, countries in the region have attempted to harmonize these to ensure better data acceptability and reduce trial and drug approval timelines.1 Malaysia is part of the ASEAN Free Trade Area (AFTA) that undertook the ASEAN Common Technical Documents (ACTD) and ASEAN Common Technical Requirements (ACTR) initiatives to standardize drug approval processes.

In Malaysia, ethics review and regulatory approvals, together with import licensing and contract negotiations, occur concurrently, allowing for faster processing timelines. These are comparable with timelines in South Korea and Singapore (approximately 2-3 months). In a recent report, regulatory timelines have been improved to within 30 working days,23 while the centralized ethics committee under the Ministry of Health has shortened its timelines to 51 calendar days.

Established infrastructure, resources, and capabilities

An established and functioning network of clinical trial centers with advanced equipment and technology, knowledgeable physicians, and available key opinion leaders in different specialties also play an important role in attracting ISRs.7 Malaysia has a well-developed and equipped healthcare system manned by medical doctors that practice and comply with international clinical practice standards.24 ISRs in Malaysia are conducted at government hospitals, teaching institutions, private hospitals, and government health clinics. Government hospitals receive and treat the largest number of patients, thus presenting a unique opportunity for access to the primary care patient pool.

Developing an ecosystem for early phase clinical research in Malaysia

The Government of Malaysia, realizing the potential positive impact of early phase trials for patients, scientific advancements, and economic growth, is stepping up its existing clinical trial capabilities by building new initiatives to drive early phase clinical research.
capacity in-country and develop an attractive early phase clinical trial ecosystem.

In lieu of this, the Malaysian government included the creation of a supportive ecosystem with the establishment of CRM, a non-profit company, wholly owned by the Ministry of Health, to equip the ecosystem of clinical research in the country. Its goal is to reach at least 1,000 clinical trials by 2020. Part of the initiatives stated in this section is to set up more research centers, develop more good clinical practice (GCP) certified investigators, and improve existing institutional review board (IRB) and ethics committee (EC) timelines. The Phase 1 Realization Project (P1RP) was aimed at realizing this aspiration of making sure Malaysia is capable in conducting early phase studies.

The benefits of conducting early phase trials in Malaysia, as laid out by the P1RP, are the increase of Phase II and III trials as a result of a spillover effect from conducting more Phase I trials, contribution to the transfer of knowledge and technologies to Malaysians, creation of new jobs in clinical research, spurring local innovation, prevention of investment outflow, and moving the country as a whole higher up the clinical research value chain. For patients, it increases the opportunity for more investigation to be made in Australia and the Philippines, as this document took into account and expanded its content to reflect the latest changes in conducting FIH trials. The Malaysian guidelines, in turn, considered local regulatory bodies and agencies’ existing procedures, and the local clinical trial environment—adapting relevant areas to facilitate the applicability of the ABPI guidelines in Malaysia.

People development
To gain knowledge and experience in Phase I clinical trials so as to implement and impart these to relevant agency officers, three regulatory officers were sent to pursue their postgraduate studies at The Christie, Manchester, as well as King’s College London, under a collaborative scholarship between CRM and the Public Service Department. This will allow them to work within a leading Phase I clinical trial unit and gain experience and understanding in the designing and delivering of Phase I studies. This attachment is important, as these regulatory officers will be the ones responsible for reviewing the dossiers of Phase I studies in Malaysia.

The Ministry of Health has also planned to send local investigators to be attached at reputable Phase I centers, including the Princess Margaret Cancer Center, to be exposed to the experience of conducting FIH studies. The government has also started initiatives to bring back Malaysians from overseas. Experts or specialists from higher-income countries returning home would have an edge due to a global mindset. Coupled with an in-depth knowledge of the country, people, and the culture, it creates a world-class pool of specialists that can support early phase trials.

To attract more specialists to participate in clinical trials, the Ministry of Health now allows for 20% of a work week (or one full day off) for investigators to focus solely on research.

The P1RP blueprint
The P1RP stands on five pillars, which are the establishment of guidelines for conducting Phase I clinical trials in the country, people development, capability development, preparation of sites, and risk management. To date, all of the P1RP pillars have been implemented and fulfilled. In the first quarter of 2019, the country’s regulatory authority had indicated that it was ready to review FIH studies.

The P1RP strategy is multi-pronged wherein regulatory agencies are equipped with the right knowledge to review Phase I clinical trials. Conforming to international standards, local experts are trained with the necessary skills to analyze early phase trials through engagement with international consultants, preparation of clinical trial units at hospitals to conduct Phase I studies, and the development of an action plan to manage and mitigate any given crisis that may occur during the clinical trial process.

Development of Phase I clinical trial guidelines
The Malaysian Phase I Clinical Trial Guidelines was launched in November 2017. Prior to this, the country did not have a specific guideline on Phase I clinical trials. The effort saw the coming together of experts and investigators in the field of clinical trials from the Ministry of Health, Ministry of Higher Education, ethics and regulatory bodies, as well as industry experts. International key opinion leaders on clinical trials were also invited as subject matter experts. The guidelines were based on the Association of the British Pharmaceutical Industry (ABPI) 2012 version of Phase I clinical trial guidelines, as this document took into account and expanded its content to reflect the latest changes in conducting FIH trials. The Malaysian guidelines, in turn, considered local regulatory bodies and agencies’ existing procedures, and the local clinical trial environment—adapting relevant areas to facilitate the applicability of the ABPI guidelines in Malaysia.

Capability development
In a 2011 report presentation of the Health Committee at the 49th Parliament sitting in New Zealand, some of the recommendations put forward to increase New Zealand’s presence in the clinical trial industry were to establish a strong intra-governmental collaboration between different ministries, ensure a culture that values research within the public health system, and requiring the Standing Committee on Therapeutic Trials to carry out all scientific reviews within 30 calendar days.

As part of the capability development pillar of P1RP, a Scientific...
Review Panel (SRP) for FIH clinical trials was established to support the Medical Research and Ethics Committee (MREC), a centralized ethics committee, in performing scientific evaluations of FIH trials undertaken by and/or conducted in clinical trial sites in Malaysia. The scope of review includes all FIH studies on new chemical, biological, and biosimilar drugs not registered in Malaysia.

The intensity of early phase clinical trials is more time-consuming requiring increased amounts of physical exams, vital signs monitoring, electrocardiogram (ECG) monitoring, and pharmacokinetic laboratory tests compared to later phase trials. The P1RP project and initiatives will harness the available resources and capabilities available within the country’s health system as well as increase its knowledge with international collaborations to ensure that Malaysia is ready to meet with the demands of early phase trials.

Preparation of sites
Sarawak General Hospital, located in a major city in East Malaysia, is targeted to be fully equipped to handle early phase clinical trials. It also serves as a template for future units to be developed in other hospitals. This hospital is already a major medical center with ready access to large patient populations, and the clinical trial center is well-equipped and operated by well-trained scientific and medical staff.

Risk management
In June 2007, the “Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products” was finalized by the European Medicines Agency (EMA). The scope of the guidance, which encompasses both biologics and new chemical entities, was recently updated in 2016 (EMA/CHMP/SWP/28367/07), and places the focus on the pharmacological characteristics of a new drug.

The document was created to support the transition from non-clinical to the early phase of clinical development and identifies influencing risk factors of a product, includes consideration of quality aspects, testing strategies, designs for FIH studies, and mitigation strategies such as initial dosing calculation and dose escalation.

Therefore, part of the P1RP initiative is the preparation and training of risk management guidelines and to manage any crisis in relation to early phase clinical trials. These include creation of a standard operation procedure (SOP) to prepare for and manage all types of crises requiring immediate attention during early phase trials (i.e., unexpected side effects from a clinical trial). The SOP is designed to also ensure that all actions are coordinated, timely, accurate, consistent, and effective in minimizing the potential for confusion, rumor, and misinformation. The overall objective of this effort is to offer support to the sponsor and processes of early phase trials in difficult situations, and to the greatest possible extent, limit potential injury to patients, consumers, or the reputation of the institutions.

ACCELERATE Project
CRM initiated the ACCELERATE project to move Malaysia’s focus further upstream to early phase drug discovery and development, utilizing readily available resources in the country. The project involves converging expertise and collaborations across agencies, clinical research industries, and universities on preclinical projects. Through this initiative, CRM has intensified collaborations with various universities and research institutes in “bench to bedside” projects. The conversion of preclinical studies into early and late-phase trials may spur discovery, local innovation, and eventually manufacturing of innovator drugs in Malaysia. Additionally, it can prevent outflow of investments and move the country higher up the clinical research value chain.

Conclusion
Malaysia’s effort through the P1RP and ACCELERATE project underlines the government’s commitment to bring the country into a new phase in the clinical trial industry. In the local context, early phase clinical trials play a key role in enhancing the capability of the country in the development of medical science and treatment of disease, as well as placing Malaysia at the cutting edge of research. To this end, the Malaysian government’s goal is to develop the country into becoming the preferred destination for industry-sponsored research.

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References
EMERGING MARKETS


Precision oncology promises a new model of cancer care where medical decisions are based on a holistic view of the patient, including their genes, environment, and lifestyle, and tailored to the molecular profile of their tumor. To date, great strides toward the paradigm of precision oncology have been made in the area of cancer immunotherapy, which boosts a patient’s own immunity to combat tumor cells. Immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapies have dramatically improved outcomes for a select number of patients, but widespread use of these treatments remains elusive.

To make personalized cancer treatment a reality for all patients, we need to reimagine the biopharmaceutical business model and drug development process, both of which have traditionally been focused on broad drug development and blockbuster medicines. New regulatory, technical, clinical, and economic frameworks are needed to ensure that the right patient can access the right therapy in a meaningful timeframe. In this article, I discuss three key challenges that must be addressed to fulfill the promise of precision oncology.

#1: Understanding and addressing mechanisms of resistance

The ultimate goal of cancer immunotherapy is to stimulate the immune system to launch a sustained attack against tumor cells. Given the complex and dynamic interactions between tumors and the immune system, achieving this is complicated.

The challenge lies in managing the delicate balance between autoimmunity and the immune system’s ability to recognize non-self. In some cases, the immune system may fail to recognize tumor cells as non-self and may develop a tolerance to them. Moreover, tumors have myriad methods for evading the immune system (see Figure 1).

Resistance to cancer immunotherapy can be categorized as primary (i.e., failure to respond) or secondary (i.e., relapse after successful treatment). Approaches for optimizing response and minimizing resistance to cancer immunotherapies include developing biomarkers to assist with patient selection or treatment monitoring, altering the tumor microenvironment, and educating healthcare practitioners on the potential for delayed response with these types of treatments. With CAR-T therapies, resistance may be due to poor persistence of CAR T-cells after infusion or due to antigen loss of the target receptor.

Given the elaborate interplay between cancer and immunity, combination therapies may be a rational approach to addressing resistance. For example:

**Figure 1.** Potential immunotherapy targets.²

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Outlining the three critical challenges that need to be addressed to make personalized cancer treatment a reality.
• Combining two immunotherapies targeting distinct immune checkpoints (see Figure 1).
• Combining an immunotherapy with chemotherapy, which directly kills tumor cells and may help activate the immune system to boost the response to immunotherapy.
• Combining an immunotherapy with targeted therapy to create a possible synergistic effect.

#2: Solving the logistics of manufacturing
Whereas the conventional manufacturing process is typically confined to a single facility, manufacturing of cell therapies requires multiple hand-offs. While the process begins and ends at the bedside, the process of genetic modification involves a complex chain of custody that blends manufacturing and administration (see Figure 2). The manufacturing process is further complicated by the fact that, unlike traditional manufacturing where the starting materials are standardized, the starting materials for cell therapies are highly variable because they are derived from patients. As evidenced by the highly publicized manufacturing hurdles surrounding the launch of Kymriah (tisagenlecleucel), meeting label specifications for commercial use is challenging, even for industry leaders. Sponsors must consider how manufacturing will evolve from a single facility, manufacturing of cell therapies requires multiple hand-offs. While the process begins and ends at the bedside, the process of genetic modification involves a complex chain of custody that blends manufacturing and administration (see Figure 2).

Figure 2. The CAR-T administration process.¹

#3: Developing innovative pricing models
Targeted therapies are quite costly in comparison to their traditional counterparts, and existing health insurance models have not been structured to reimburse for these types of treatments.¹ The pricing model for CAR-T therapies may be especially challenging for commercial insurers, which typically have higher turnover and shorter coverage windows than national health insurance programs. Value- or outcomes-based pricing models represent one approach to addressing the challenge of reimbursement. These new pricing models will rely heavily on patient selection, and sponsors will need to develop tools for identifying those patients who are most likely to respond to particular precision medicines.²

Notably, the Centers for Medicare & Medicaid Services (CMS) recently finalized their decision to cover FDA-approved CAR-T therapies when provided in healthcare facilities enrolled in FDA risk evaluation and mitigation strategies (REMS) for FDA-approved indications. Medicare will also cover FDA-approved CAR-T treatments for off-label uses that are recommended by CMS-approved compendia.³

Realizing the promise of precision oncology
The precision medicine market is expected to exceed $96 billion by 2024, with the oncology segment leading the way.³ Patients, providers, and advocacy groups are pushing for innovation, but precision oncology is still in its infancy and significant challenges remain. As advanced technologies and data analytic techniques are increasingly incorporated into the drug discovery and development process, the hope is that precision oncology will not only enable the personalization of cancer drugs, but also improve population health as new genetic and molecular insights enhance our understanding of the mechanisms of disease.

References
Participant safety is the clinical trial sector’s top priority—and striving to achieve this laudable aim also makes for more agile, flexible, and efficient studies. That’s what we learned from a second executive roundtable discussion, hosted by the Tufts Center for the Study of Drug Development (CSDD), and supported via an educational grant from CluePoints and PricewaterhouseCoopers, on the progress the industry is making toward implementing the requirements of the ICH E6 (R2) addendum.

At the starting blocks

When it was introduced in 2017, ICH E6 (R2) represented the biggest change to international clinical research in two decades. Developed as a response to the rising complexity of studies and the industry’s increasing reliance in electronic data management and reporting systems, the update sought to define good risk management in the modern trial environment. It states that clinical programs should implement risk assessment at both the trial and system levels and that metrics on clinical monitoring and data management should be captured in preparation for clinical study reports.

Following the addendum’s publication, Tufts CSDD held the first roundtable on the updated guidance and found companies in the early stages of a big change. Kenneth Getz, former director of sponsored research and research associate professor at Tufts CSDD, who was recently promoted to research professor and deputy director, organized and facilitated the event with colleague Yaritza Peña, a research analyst at the center.

“Two years ago, companies were in the early stages of interpreting the guidance to translate recommendations into tangible operating practices,” said Getz. “Roundtable participants indicated their initial focus was largely on risk-based monitoring (RBM). They were beginning to implement risk assessment procedures to identify which operating practices were most impacted. Although apprehensive about how the addendum would affect their current standard operating procedures (SOPs), the attendees had all agreed that the revised guidance was a step toward more agile, flexible, and efficient clinical trials,” he added.

Embracing change

These latest discussions, held in Boston in April, found that the organizations had made significant progress on a granular level, and were now taking a more holistic view. A total of 41 participants from organizations including Alkermes, GlaxoSmithKline, Pfizer, Roche-Genentech, Sage Therapeutics, Takeda, the Metrics Champion Consortium (MCC), and FDA took part.

After a panel discussion about ICH E6 (R2) compliance, the companies offered up their own examples before addressing the barriers and anticipated direction of travel. They found that rather than focusing simply on RBM, the industry has been working toward improving study efficiency overall, by taking a much broader view of risk-based approaches to study execution, or RBx.

“Company mindset has progressed from 2017,” said Peña. “Since then, many organizations have incorporated a risk-based framework across end-to-end development processes. Companies are refining the quality management plans developed during the planning and execution stage, and using technology to drive pattern identification, machine learning, and study-specific analysis.”

The discussions found that new regulations had compelled companies to move away from a clinical research associate (CRA)-centric, on-site visit model of moni-
Challenges and opportunities

Companies chalking up success in this area are those that have recognized the opportunity and have since worked to reorganize SOPs and pathways to allow for a portfolio, rather than a program-wide view. They are making significant investment in analytical capabilities that not only apply to RBM and oversight, but also to operational outcomes such as enrollment and protocol feasibility. Advanced data visualization, for example, can automatically detect trends and anomalies, and automated query management systems assist with the reconciliation of serious adverse events.

Study optimization is a natural consequence of utilizing these metrics, which allow companies even more sophisticated ways to distinguish between reliable and potentially unreliable data, and to avoid unnecessary protocol complexity. These opportunities are only set to increase as analytical techniques, including machine learning, natural language processing, and other types of artificial intelligence (AI) are put to use in the clinical trial space.

Achieving this holistic approach isn’t without its challenges, and integrating ICH E6 (R2) concepts into study planning and implementation is proving difficult for some sponsors. “Part of the challenge depends on the creation of an efficient interface between a proactive quality planning process and a risk-based monitoring process,” said Getz. “Another daunting task is shifting company culture to adapt to the necessary changes to study processes when anticipating risk and performance issues.”

Getz further explained: “Since risk management is not currently a core operational competency, employees require training and monitoring to understand concepts such as data quality vs. data integrity, site monitoring vs. trial monitoring, and data reliability vs. trial results reliability.”

According to the panelists, the companies currently embracing the opportunities of RBx have fundamentally changed the way data are verified, reviewed, analyzed, and managed within their organizations. This has taken commitment from senior leadership and a wholesale change both in company structures and culture. Strategies employed have included robust change management training and the digital upskilling of staff. Clinical study teams, tasked with examining ICH E6 (R2) requirements to ensure the right data quality oversight tools are being used, have also been set up.

Some industry players have developed teams of subject matter experts (SMEs) with the responsibility to ensure the updated guidance is implemented. These SMEs are able to take an overarching view of risk identification, reporting and evaluation, cross-functional sharing of risk, and the monitoring of risk control measures across studies and protocols.

“Another daunting task is shifting company culture to take in the bigger picture, is the key to realizing the potential of RBx,” said Hayden. “The main drivers in successfully implementing a risk-based approach to study execution is to consider the interconnected nature of risk identification and analysis throughout the entire lifecycle of the clinical program.”

What’s next?

While many of the companies at the roundtable said the project had increased operating costs, they also said these were offset by the benefits in terms of risk mitigation and proactive decision-making. As clinical trials become ever more complex and fragmented, RBx systems can be used to continue to consolidate and streamline studies while allowing for strategic oversight. In fact, many of the roundtable companies said they believed they were better placed to drive effectiveness and optimize performance in the next three to five years.

Those with the framework of RBx “in situ” appeared best placed to leverage the rich data that will be generated by ever-advancing analytics. While AI utilization is still in its infant stages, for example, the roundtable participants expect it will soon play a role in efficiently identifying areas of risk and be able to guide stakeholders to the best possible solutions. They are also in the best position to respond to expected regulatory changes—FDA is currently looking at revisions for E8 as well as a proposal regarding the next iteration of E6, for example.

“Drug development sponsors are being encouraged to partner with regulators, take more innovative risks, and amplify their concerns and ideas in terms of clinical trial quality and compliance,” said Peña. “With more time to process learnings from new technological implementations, the industry will begin to see additional standards for proactive clinical trial planning, execution, and quality-by-design.”

In the long-term, companies will save time and expense from identifying anticipated risks early on through the refinement of current processes, she added.

RBx is about investing in the future by improving quality and effectiveness. Roundtable attendees agreed that while holistic ICH E6 compliance has led to a modest increase in short-term operating costs, they expected to see substantial savings over time.

Investing in the risk-based approach to the design and conduct of clinical trials is about the intelligent use of data to make informed decisions. It’s not only sponsors and CROs that are adopting risk-based approaches, but regulators are as well.
China: A New Era of Drug Development and Innovation

The focus of China’s drug development landscape, continuously center stage in industry discussions, is not only on including China in global clinical trials, but also on how its biotech companies are emerging as serious global competitors. China has always been a key focus for multinational biopharma companies. As Asia’s largest market and global patient pool for many diseases, it accounts for 19% of the world’s population (with 22% over age 65). China’s healthcare providers treat three to four million cancer patients annually, while the country has 110 million diabetics and another estimated 500 million pre-diabetics.

Even though these statistics suggest opportunities exist for global companies to introduce innovative therapies into China, regulatory complexity and timelines historically have excluded or delayed China’s involvement. China’s National Medical Products Administration (NMPA) began to overhaul the country’s regulatory landscape in 2018. Significant changes have taken place, including an improved drug review process; shortened investigational new drug (IND) and new drug application (NDA) review timelines; acceptance of clinical data from outside China; and International Council on Harmonization alignment and integration.

As regulatory pressures recede, other challenges have become more prominent. One example is an industry talent shortage and the scarcity of qualified and experienced clinical trial sites. China can only field about 800 qualified centers to run clinical trials, compared to more than 10,000 in the U.S. As a result, there is competition for available sites and principal investigators.

Additional challenges for non-Chinese companies including China as a participant in global development programs are the potential treatment paradigm, language, and cultural differences. Standard of care or referral routes can be quite different in China versus the rest of the world. Performance endpoints also can be affected due to cultural influence on variables such as patient-reported outcomes or physician assessments.

China’s biotech boom

China’s biotech industry is also entering a new phase of innovation. In 2018, China contributed to 7.8% of the global drug innovation pipeline and 11.6% of new drug launches. Chinese biotech and pharma companies now also are sponsoring global clinical trials. For instance, there are 50 IND applications by Chinese companies in the U.S. compared to single-digit numbers five years ago. Many Chinese pharma companies have focused on generics, but domestic drug pricing and reimbursement reforms are reducing drug prices and encouraging generic drug industry consolidation.

Adapting to the global market

Many Chinese drug developers running trials outside their country face considerable challenges finding the right CRO partner—one who possesses the global expertise and cross-cultural understanding to help them bridge societal differences. Team chemistry is a crucial factor affecting sponsor–CRO relationships, as teams must work closely and relate to each other for extended periods of time, often on projects involving multiple countries and large investments. Conversely, CROs must be cognizant of sponsor cultural differences and adjust their business practices.

At the same time, Chinese biotech companies should adapt their practices through a more holistic approach to their development programs and strategic planning, as their commercialization strategy should look beyond FDA or EMEA approval. Unlike the U.S. and Europe, the Chinese pharma market historically has not required healthcare outcomes data for reimbursement, but it’s now common practice for pharma and biotech to incorporate this research into their clinical development programs for future value dossier development. Another way to place China’s drug development industry on par with the rest of the world would be to develop a viable means to establish competitive prices, especially on cancer drugs such as PD-1 inhibitors.