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Volume 27 Number 5 May 2018

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

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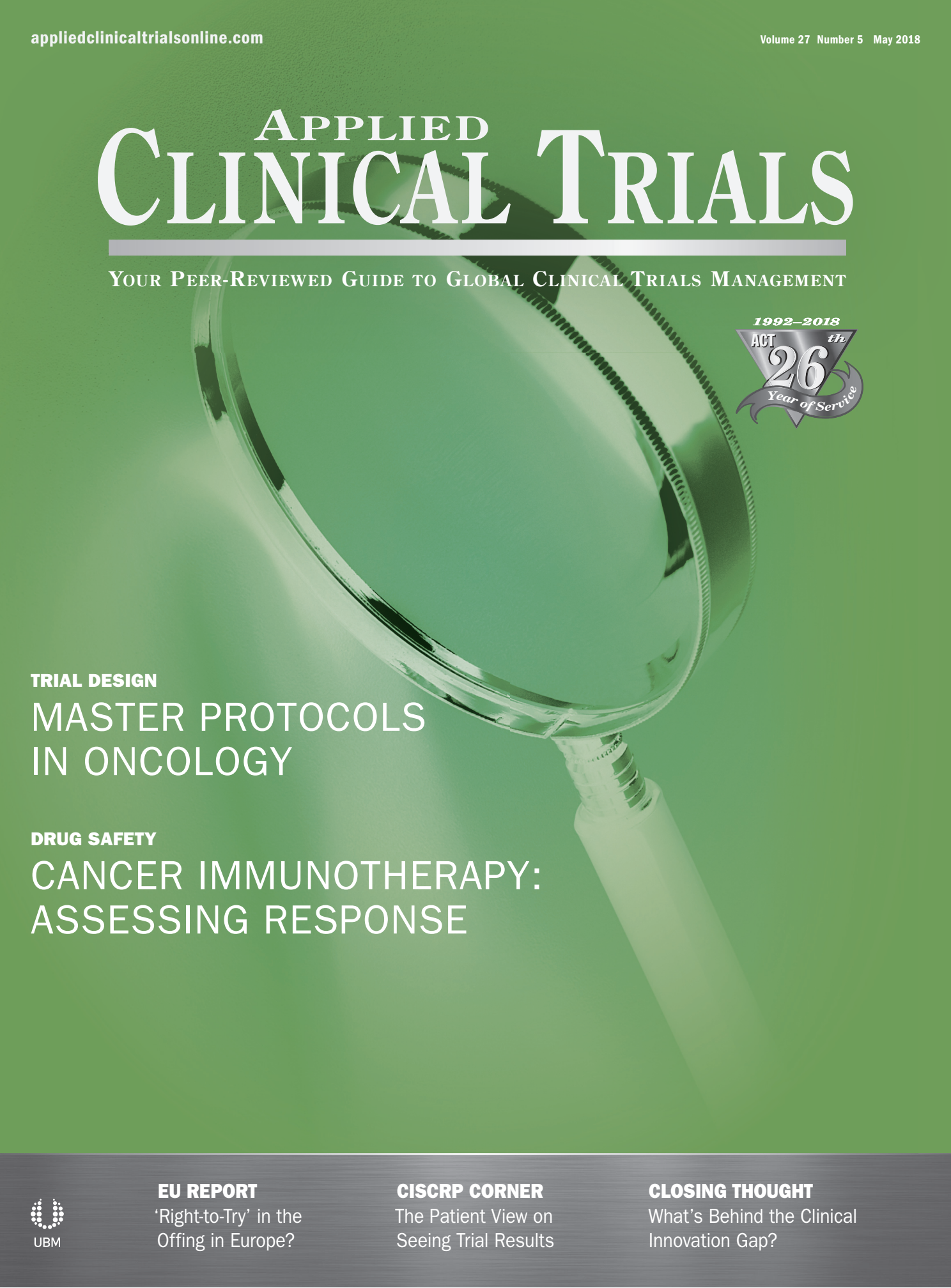

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What's Behind the Clinical Innovation Gap?

Awareness for Clinical Trials as a Care Option

LISA HENDERSON
Editor-in-Chief

The efforts to get more visibility for clinical trials awareness, and to offer it as a care option, continue this May with a number of events.

Although this letter won't be available until after this event takes place, it is one that the Coalition for Clinical Trials Awareness has supported for a number of years, the Clinical Trials Awareness Week (bit.ly/2FkF0Nh). This year, it was celebrated April 30-May 4 and included a Tweet Chat on May 2 and a visit to Capitol Hill May 1. Along with the National Coalition for Infant Health, a panel discussion was scheduled to focus on the challenges in recruiting infants and children for clinical trials and the subsequent gap in new therapies for the neonatal population. Topics also slated for discussion included the need for incentives to improve the gap in medical innovation for infants and children, and an update on the Promoting Life Saving New Therapies for Neonates Act (H.R. 2641).

On May 19, the Center for Information and Study on Clinical Research Participation (CISCRP) is holding its popular AWARE for All event in Los Angeles at the USC campus. AWARE for All is a free educational program that provides valuable information and resources on the clinical research process to help people make informed decisions about participation. The event serves as a platform for dialogue between local patients, members of the public, and research professionals. Leading up to the event, the AWARE for All Journey to Better Health Mobile Unit will be traveling around Los Angeles with an interactive, experiential mobile unit to educate the public about clinical research (bit.ly/2r376aH).

International Clinical Trials Day is celebrated every year on May 20 to bring the global clinical trials community together for communications, events, meetings, debates, and recognition on clinical research. It is celebrated on May 20, to recognize James Lind, a Scottish physician who first studied scurvy in a systematic experiment on that day in 1747. Because he equally divided sailors into groups that tested different treatments against scurvy, with all having the same diet, it is one of the first reported, controlled, clinical experiments in medical history.

Another event, to be held on May 31, is the final gala event to celebrate the PopUp Star clinical trial awareness contest. You can learn more here: bit.ly/2vU6oSN, but the premise is that all healthcare stakeholders can impact awareness for clinical trials as a care option with grassroots community-based events and planning. #PopupStar submissions have already closed and the three finalists will be brought to New York City for the award ceremony and live broadcast of the winning team announcement. *Applied Clinical Trials* will be in attendance to help spread the word of clinical research as a care option.

In addition, the @OnePersonCloser campaign I wrote about in March (bit.ly/2vU6Y2V), and the Bridging Clinical Research and Clinical Care event I covered (bit.ly/2KlaeaM) continue discussions and feedback in earnest.

I learned quite a few good ideas about communicating the value of clinical trials at the Bridging Clinical conference. One was that at one hospital, they wore button pins that said, "Ask Me About Clinical Trials." This one small effort did translate into trial awareness. In our own ways, those of us in the industry can do small efforts (or big ones) to bring trials closer to patients.

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

APPLIED CLINICAL TRIALS
VOLUME 27, NUMBER 5

GETTY IMAGES/IMAGE SOURCE

PEER REVIEWED

10 Master Protocols in Oncology

Bradley Smith, Kathy Giusti, Richard Hamermesh, Dixie-Lee W. Esseltine

With technology's increasing ability to gather and analyze previously unmanageable data sets, and medicine's forays into genomics and targeted therapies, the time of the master protocol may be at hand.

PEER REVIEWED

NEWS AND ANALYSIS

COMMENTARY

WASHINGTON REPORT

GOTTLIEB SEEKS MORE EFFICIENT CLINICAL RESEARCH STRATEGIES TO LOWER DRUG COSTS

In his first year leading the FDA, Commissioner Scott Gottlieb has promoted multiple initiatives to streamline drug development and clinical research as part of his campaign to moderate drug prices and achieve "a good balance between innovation and access," he told *Applied Clinical Trials* magazine in a recent interview. The commissioner has blasted brand manufacturer "shenanigans" for blocking generic drug approvals, while also supporting the development of more effective pain medicines and addiction treatments to help combat the lethal opioid epidemic plaguing the nation.

In tackling contentious issues, Gottlieb has quieted critics on all sides. Democrats initially feared an industry bias, but have been impressed by his efforts to advance public health and challenge drug prices. Republicans hoping for a free-market deregulator support his campaign against opioid abuse and efforts to speed innovative drugs, devices, and diagnostics to patients.

A clear sign of achievement for Gottlieb is the $400 million boost in FDA's budget plan for 2019, a notable shift from earlier administration proposals to sharply cut agency appropriations. To convince the legislators to approve the requested funds, FDA has outlined how the added resources will advance biomedical innovation (see bit.ly/2JXjcum). A prime initiative is to develop data and analytical tools to better utilize real-world evidence in accelerating medical product development. An expanded "knowledge management system" will evaluate new drugs more rapidly and consistently. Additional funds will support FDA's Oncology Center of Excellence and advance new treatments for rare diseases.

FDA also faces numerous deadlines for implementing the 21st Century Cures legislation, including provisions to support regenerative medicine and to speed the development of new cancer treatments, personalized medicines, and gene therapies. At the other end of the spectrum is a proposal for new user fees to support more efficient oversight and approval of over-the-counter drugs.

More guidance

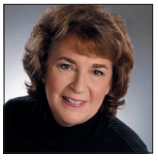
FDA will be hard pressed in the coming months to realize last year's gains in drug development and approvals, while also tackling a number of hot issues, such as nicotine levels in cigarettes, oversight of independent testing labs, and food contamination outbreaks. A main strategy for the commissioner is to take some of the innovative research approaches devised for the oncology setting and implement them across additional new drug review divisions, Gottlieb told ACT.

This involves developing guidance documents on strategies such as designing master protocols and shorter advisories on applying different clinical trial approaches to additional disease settings. In February, for example, FDA issued several guidances on addressing serious, complex neurological conditions, such as Alzheimer's disease (see bit.ly/2qKfzjJ). Gottlieb also unveiled in March an updated Benefit-Risk Assessment plan for incorporating patient perspectives into regulatory decision-making (see bit.ly/2HE9sHr). More recently, FDA published draft guidance on including pregnant women in clinical trials (see bit.ly/2J8dKnd) and an update on international standards for pediatric drug development (see bit.ly/2JarpdA). A final guidance clarifies FDA's process for sponsors to gain FDA agreement on development programs under the special protocol assessment (SPA) process (see bit.ly/2HLrUvh). And the agency proposed in April a model-informed drug development (MIDD) pilot program, with a series of workshops, to encourage sponsor use of exposure-based, biological and statistical models in drug development programs (see bit.ly/2qLado4).

Gottlieb anticipates that more streamlined clinical research and disease-specific guidance, along with initiatives to speed more generic drugs and biosimilars to market, should translate into lower drug costs. While the commissioner acknowledges that new drugs are priced at what the market will bear, he believes that more predictable R&D pathways can help "de-risk" drug development, which would reduce the cost of capital and permit a lower price to justify initial R&D investment. Such efficiencies may be even more important in bringing a second or third branded product to market, which Gottlieb considers important for achieving a good balance between innovation and access.

A related intriguing issue for Gottlieb is how current policies and practices encourage global "free riding" on U.S. biopharmaceutical R&D. New FDA data indicates that other industrial nations pay more for generic drugs than in the U.S., and less for innovator therapies—"but not a lot less" when adjusted for net price, he points out. The payments should be reversed, Gottlieb says, as the current situation is a "recipe for destroying innovation."

Gottlieb's concerns about the high cost of medicines reflect his own experience as a physician and seeing ill patients "struggling very hard at the worst moments in their lives" to try to afford drugs that are "absolutely indicated for their disease." He wants to be sure "that in my time here at FDA, I do something to address that."



— Jill Wechsler

FDA NEWS NOTES

The following committee meetings are scheduled for May:

- Endocrinologic and Metabolic Drugs Advisory Committee Meeting ***May 10***
- Joint Meeting of the Pediatric Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee Meeting ***May 11***
- Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting ***May 22***

EU REPORT

'RIGHT-TO-TRY' SCOPE EXPANDING TO EUROPE?

Renewed attempts in the U.S. to win legislative approval for the right-to-try concept have again focused attention on that inevitably grey area between hoping a new medicine is going to be effective and demonstrating that it can be. As the debate highlights so sharply, patients in desperate straits are likely to be more inclined toward hope than insistent on demonstration. Regulators find themselves constantly challenged to defend their own red lines in what is a constantly shifting context, where technology and scientific innovation demand perpetual reassessment of the decision-making rationale.

Europe is not so far down the track as some US legislators and pressure groups. Access to unlicensed medicines is provided for, of course, via compassionate use and on a named-patient basis, but divergent national reticences persist. A young British epileptic patient responsive to cannabis oil prescribed in the Netherlands is currently fighting the UK authorities for access to what Her Majesty's Government deems a prescribed drug.

An additional light has been shone on the debate by a strongly-worded statement from Belgium's feisty health minister, Maggie De Block. Now the Belgian authorities find themselves swept up in the controversy, after reports that De Block had suggested to the girl's mother that she should move abroad to obtain the treatment.

De Block flatly denies having advised the mother to take the child to a different country in pursuit of cannabis oil. But more interestingly for the wider world, the minister goes on to make a strong defense of the concept of government action to protect the public against unlicensed treatments.

While cannabis oil may help some children, she conceded, "it is very harmful, and even deadly, for others." She expanded on that specific point to draw a broader generalization: "That's why we need irrefutable evidence that cannabis oil is safe for health and its effects are beneficial for everyone."

De Block was careful to take account in her argument of some of the tensions underlying the provision of novel treatments. She noted that cannabis can be marketed as a licensed drug for the treatment of some specified conditions, such as to treat spasms and pain in multiple sclerosis.

But, she added, the unfortunate reality is that unmet need continues to exist. Effective pain relief is not available for all cases and conditions, and "international drug research is not always progressing as quickly as we would like. It often takes a very long time to reach a scientific breakthrough." Her conclusion is crystal clear—and will offer some comfort to drug developers facing dirigiste pressures from regulators or governments keen to dictate research agendas.

Little movement on MAPPs

The European discussions about earlier access are taking place in the somewhat tamer framework of adaptive pathways, or MAPPs—as this blogger noted in February ("Removing the risks from adaptive pathways: planning for the possible?"). The EU's ADAPTSMART project, which has been exploring the feasibility of MAPPs for the last three years, reached its climax in late March at a closing conference in Budapest, where the benefits and the challenges were given a gratifyingly candid airing.

Everyone there agreed on the merits of access to beneficial treatments for specific, well-defined, patient groups with a high unmet medical need at the earliest appropriate time in the product life-span in a sustainable and affordable fashion. More realistically, Hans-Georg Eichler, senior medical officer of the European Medicines Agency (EMA), and one of the key figures in European MAPPs, claimed some progress in promoting an evolution of mindset so that the approval of needed medicines is no longer seen in a standard linear approach, but at the same time acknowledged that "this opinion is not unanimous."

According to Wim Goettsch, the special health technology assessment (HTA) advisor for the Zorginstituut Nederland, and an early advocate of MAPPs, "the acceptance of MAPPs amongst many HTA bodies is low"—so much so that he posed the question "Is MAPPs deceased?" And Francesca Cerreta, scientific administrator of the EMA, said: "We have some remaining uncertainties."

In addition to widespread hesitancy over the concept of MAPPs, there is a formidable list of evident and immediate concrete challenges, including the lack of an agreed definition for high unmet medical need, insufficient systemization of real-world evidence, gaping infrastructure deficiencies, and establishing a coherent link between the regulatory issues of authorization and the economic issues of payment.

Valentina Strammiello of the European Patients' Forum pointed to gaps in national capacities for collecting real-world data, and Jacoline Bouvy of NICE commented that "the responsibility of collecting the data will fall to healthcare professionals, and they are already saying they are over committed for time and resources." Just as crucially, while some HTA bodies are willing to use real-world evidence to make assessments, others are not. According to Goettsch: "We've had many experiences where we've asked companies for real-world evidence and the data we get is not what we wanted. For MAPPs to work, the data needs to be addressing the endpoints where we expect evidence."

Industry concerns as well were recorded about the need to commit both to a smaller first population at the start of the 10-year exclusivity period, with potential limits to revenues over time, and to a requirement to generate evidence over the long-term. Solange Corriol-Rohou of AstraZeneca, a key figure in ADAPTSMART, admitted that MAPPs "still is a highly sensitive and controversial concept," and could offer the meeting the reassurance only that "We try to have broader collaboration with payers and healthcare providers." But the President of the Dutch Medicine Evaluation Committee, Ad Schuurman, expressed disappointment that "so far, none of the companies seem willing to come forward and try to do MAPPs for real."

The conference did agree on a series of action points, covering some of the unresolved issues—from evidence collection to payment methodologies, and from involving payers more actively in discussions to setting up MAPPs pilots. The European debate, currently, is more about the right to try MAPPs than the right to try unlicensed medicines.

— Peter O'Donnell

CISCRP CORNER

PATIENT PERCEIVED IMPORTANCE OF RECEIVING STUDY RESULTS

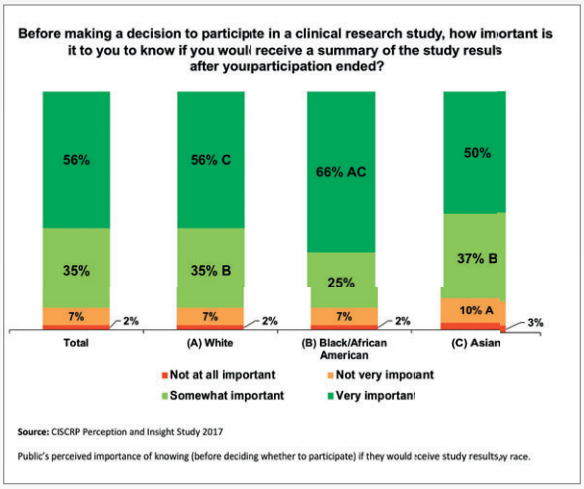
This article is the third in a series on the results from the Center for Information and Study on Clinical Research Participation's (CISCRP) 2017 Perceptions & Insights Study.

Conversation Starters

When patients around the world are asked what they perceive to be the greatest benefit of participating in a clinical research study, they rank altruistic reasons such as the ability to help advance science and the treatment of a disease (26%) or to help save or improve the lives of other patients living with the same disease (26%) the highest. The third-greatest benefit they mention is the chance to improve one's own disease or condition (15%). While clinical trial sponsors are unable to guarantee that a study drug will be effective and improve one's condition, they can take steps to make patients aware of their contributions in these areas and convey that they are a valued research partner. A critical initial step is providing patients a summary of the general study results to allow them to better understand how their participation contributed to the development of a new medical therapy. Eventually, sponsors will share patients' individual studies to help inform how the study medication may be impacting their condition.

Knowing whether or not one will receive a study summary at the end of the individual's participation is an important factor in the decision to participate in a clinical trial. An overwhelming majority (91%) of patients feel this is "very" or "somewhat" important. African American patients are the most likely to rank knowing whether they would receive a summary of their study results before making a decision to participate as "very important" (66%) when compared to White (56%) or Asian (50%) populations. This suggests that mistrust still exists within this particular population. Sharing trial results could be a new way to build trust and to help this community feel more informed about the benefits and risks of their participation and to ultimately increase engagement.

When asked what information patients would be the most interested in receiving during their participation in a clinical trial, individual study results (73%) and a summary of the study results (72%) are listed as the top two pieces of information by the general population. North Americans are more likely to find it "very important" to receive this information than other regions, perhaps due to an increased desire to be more proactive with their own health. Additionally, patients over 55 years of age are also more likely to want to receive their individual study results (77%) than younger patients (67%), possibly because older people are more likely to be living with a condition.



There is also evidence suggesting that the severity of one's condition shapes expectations in terms of what these patients hope to get out of clinical trial participation. People who report living with very severe conditions are significantly more likely than healthy volunteers to participate in a study because it would help advance treatments for the disease they were managing (73% vs. 33%), or help them obtain better treatment for their condition (70% vs. 8%). Furthermore, patients who rate their condition to be very severe are more likely to mention that it is "very important" to receive a summary of their individual study results (73%) when compared to healthy volunteers (60%). The significance this population places on receiving study results may stem from their heightened desire to identify an effective treatment for their condition and their ability to empathize with others living with the same condition, which would, in turn, peak their interest to see how much of an impact their participation in a clinical research study was making on the treatment of the disease as a whole.

Even though there is substantial evidence that both pharmaceutical companies and patients would benefit from the sharing of clinical trial results, only 30% of those who participate in a study report ever having received a summary of the study results at the end of their participation. Interestingly, patients who participate in Phase I studies report receiving study results more often than do patients who participate in later study phases. This could be due to a lack of therapeutic benefit for Phase I participants since they are usually healthy and participating for purely altruistic reasons, or because of the lower volume of patients involved in these trials, making it easier for sponsors to gather and disseminate this information.

The "So What?"

The disparity between patients' desire to receive study results and the low frequency at which they actually receive them highlights opportunities to make patients more informed about the benefits and risks of participation at various stages of their clinical trial experience. It additionally communicates to the patient that the study staff appreciate their participation, and are making an effort to respect them as a valued research partner. Patients who report having received updates on the results of the study at the end of their participation are significantly more likely to report that they "trusted pharmaceutical companies a lot" (30%) to give full and accurate information about the health risks and benefits of new medicines than do those who report not receiving results once their trial participation was over (23%). By providing patients with their clinical trial results, pharma companies can address the motivations that make clinical research participation meaningful to patients, as well as help build the public's trust in the clinical research enterprise.

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

LEARN MORE ABOUT

MEDICINE USE AND SPENDING IN THE U.S.

A Review of 2017
and Outlook to 2022

The IQVIA Institute for Human Data Science released its annual *Medicine Use and Spending in the U.S. A Review of 2017 and Outlook to 2022 Report* on April 19, 2018.

Spending on medicines remains a topic of intense interest among policy makers, patients, payers and drug manufacturers. The level and growth of spending, the prices of drugs, and the allocation of costs among patients, employers, health plans, intermediaries and state and federal government agencies all command great attention. A wide number and range of statistics are used in public discussion of these issues, but the lack of transparency and consistency of these measures reduces the opportunity for meaningful and evidence-based debate.

The IQVIA Institute report uses research, analysis and data to provide objective measures of medicine use and their costs to the U.S. healthcare system.

Webinar discussion topics will include:

- Net manufacturer drug revenues after discounts and rebates
- Patient out-of-pocket costs at pharmacies
- Overall volume of medicines being used, with a special focus on prescription opioids
- The remarkable number of innovative medicines launched in 2017
- An outlook through 2022 for the pharmaceutical market

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Q&A

BMS AND BIOMARKER RESEARCH

Biomarker research is transforming how the pharma industry approaches a number of challenging therapeutic areas. In oncology, predictive biomarkers have played a pivotal role in evolving what was once primarily a chemotherapy, one-size-fits-all approach to treatment into a personalized approach based on a person's individual tumor biology.

Translational medicine plays a critical role in advancing this emerging field of research. By providing R&D departments with the capabilities to generate better hypotheses, implement new insights in clinical trials, and accelerate their pipelines, biomarkers have been able to quickly impact the treatment landscape for patients. At Bristol-Myers Squibb (BMS), researchers are using predictive biomarkers to help identify and develop targeted treatment approaches for patients who are resistant to current immuno-oncology (I-O) therapies.

Ahead, Saurabh Saha, MD, PhD, senior vice president and global head of translational medicine at BMS, shares his perspectives on the current biomarker landscape, the role of translational medicine in accelerating this area of study, and how BMS is working to advance biomarker research across their R&D portfolio.

Q: Can you outline the current opportunities and advancements in the biomarker market?

SAHA: Within the I-O arena, we're actively evaluating multiple biomarkers to better understand their potential in predicting how a patient may respond to I-O treatment. We are also investigating biomarkers across other therapeutic areas, including a propeptide known as PRO-C3 as a potential biomarker for nonalcoholic steatohepatitis (NASH), which currently can only be diagnosed through an invasive liver biopsy, and anti-citrullinated protein antibodies (ACPA) that may help physicians diagnose rheumatoid arthritis before joint damage becomes clinically apparent.

Q: What key challenges remain in translational medicine?

SAHA: Translational medicine includes all of the activities that are necessary to profile a patient's disease biology so we can provide the patient with as many treatment options as possible, and to increase both the speed and success of our drugs through the clinic.

Every patient has a unique disease biology, which means there are no one-size-fits-all approaches to treating many conditions. Even with biomarkers in I-O, there is no single marker that will tell us everything; it will vary depending on the type of cancer and the status of that tumor.

Another challenge is that in order to help streamline clinical trials and develop safe and effective therapies at a faster rate, we need to continue finding new ways to generate more actionable, testable hypotheses, while focusing our efforts on the ones most likely to succeed.

Q: What distinguishes BMS's activities in this area from what you've seen in your previous roles?

SAHA: I believe what makes Bristol-Myers Squibb unique is that we invest an enormous amount of time and resources across all areas of translational medicine and push the boundaries of science. Additionally, our translational medicine team is truly a core group. Every area, from translational pathology to bioinformatics, is fully integrated across our discovery and clinical development teams, which allows for rapid, efficient knowledge-sharing and collective idea generation.

Q: As global head of translational medicine, can you outline how your activities will have global reach?

SAHA: I am responsible for overseeing our robust translational medicine program and driving early clinical development across the pipeline, with the goal of driving new compounds to clinical trials, and hopefully one day, regulatory approval. Given Bristol-Myers Squibb's global presence, I have an excellent opportunity to drive our research and development efforts worldwide.

Q: Collaboration is of course key to translational medicine. How do you see BMS and pharma, in general, furthering its collaborative initiatives in this field?

SAHA: Solving the puzzles for challenging diseases will require a collaborative effort across multiple sectors.

Saurabh Saha

Photo: Jen Randall Photography

At BMS, we have more than 75 active partnerships and collaborations with academic research centers, laboratories, clinical trials organizations, and biotech firms, which complement our unique translational medicine offering. One great example of this is the International Immuno-Oncology Network (II-ON)—one of the first peer-to-peer collaborations to bring industry and academia together—which aims to advance I-O science and translational medicine through innovation. Since Bristol-Myers Squibb formed the network in 2012, the II-ON has produced data from a plethora of research projects and launched 14 biology-driven clinical trials across 22 different tumor types. Insights from these data have led to several published papers and even some of the earliest findings on a number of biomarkers.

Another example is our participation in the Accelerating Medicines Partnership (AMP). This consortium of industry, academics and the National Institutes of Health (NIH) came together to develop new ways of identifying and validating promising biological targets for diagnostics and drug development. Through the AMP RA/SLE program, we are working with the partners to address relevant challenges for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), two key areas of focus for Bristol-Myers Squibb. The data generated from this research will be publicly available, and could potentially be applied to diseases beyond RA and lupus.

In the future, I imagine the focus on collaborations will continue to become more important as we work to generate insights as a collective research community. By working together, both pharma and its partners can play an essential role in advancing novel, translational science.

— Staff Report

REGULATORY

FDA EXAMINES ELIGIBILITY CRITERIA IN TRIAL DESIGN

Efforts to devise more informed and productive clinical research programs, while also addressing demands for expanded access to experimental therapies, has focused attention on the role of inclusion/exclusion criteria in clinical research. Sponsors design clinical trials to demonstrate efficacy of a drug on a target population, usually including sufficient subgroups to support broader product use. More innovative and adaptive trial designs may facilitate including certain rare disease populations and demographic minorities that also may benefit from treatment, but with an eye to avoiding requirements that could add to the cost and challenges in conducting necessary studies.

FDA is exploring these issues, as discussed at a recent public workshop on Evaluating Inclusion and Exclusion Criteria in Clinical Trials in Washington, D.C., organized by the Duke Margolis Center for Health Policy in collaboration with FDA. While these issues have been reviewed frequently in the past, recent legislation authorizes further assessment of FDA eligibility policies and of National Institutes of Health (NIH) research standards.

The experts at the Duke workshop noted that while more restrictive eligibility criteria may be appropriate for early stage clinical trials when little is known about product safety and efficacy, enrollment of more diverse populations is desirable for later studies to help ensure that a therapy is approved for all patients likely to benefit. Restricting patient enrollment may prevent generalizability of study findings to broader populations, limit development of risk and outcomes information for certain groups, and undermine reimbursement and coverage decisions by health plans and payers.

The regulators and research community thus are reexamining enrollment criteria for clinical trials to avoid underrepresentation of relevant populations and to assess how eligibility criteria impact patient access to investigational drugs. Robert Temple, deputy director for clinical science at the Center for Drug Evaluation and Research (CDER), reviewed the trade-offs for sponsors in limiting variability in study populations. He noted that FDA has long advised against excluding particular subgroups such as the elderly and women and that labeling for new therapies requires information on subgroup differences in indications, dosage, and adverse reactions.

Including older individuals in clinical trials also is important in gaining coverage for Medicare populations, and the Centers for Medicare and Medicaid Services considers these issues in assessing reimbursement for new drugs and medical products. As part of ongoing NIH review of whether its policies sufficiently support the inclusion of all ages in funded research, as required by the 21st Century Cures legislation, an agency task force organized a workshop in June 2017 on inclusion of patients of varying ages. That has led to policy revisions requiring that all NIH-funded projects include a plan for including pediatric populations.

— Jill Wechsler

NEWS NOTES

CSDR PARTNERS WITH MAJOR NON-PROFITS

ClinicalStudyDataRequest.com (CSDR), the online resource giving researchers access to patient-level clinical trial data from 14 of the world's leading pharmaceutical companies across multiple therapeutic areas, has entered into new strategic collaborations with four major non-profit partners: The Bill & Melinda Gates Foundation, Cancer Research UK, Medical Research Council, and Wellcome Trust. The new consortium partners expand CSDR's ability to deliver upon its promise to help accelerate life-saving discoveries and efficiently translate big data into smart data that generates valuable research results. CSDR allows access to de-identified patient data from more than 3,500 studies worldwide.

Immunological platform pact

Gilead Sciences and Verily Life Sciences LLC have struck a collaboration using Verily's Immunoscape—a platform for generating immunological data and insights—to identify and understand the immunological basis of three common and serious inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease, and lupus-related diseases. Verily will analyze biological samples and clinical disease and treatment response data from patients participating in current and future Gilead clinical trials.

GSK transfers RD gene therapy portfolio

GlaxoSmithKline and Orchard Therapeutics inked a strategic agreement, under which GSK will transfer its portfolio of approved and investigational rare disease gene therapies to Orchard, securing the continued development of the programs and access for patients. GSK will continue to invest in the development of its platform capabilities in cell and gene therapies, with a focus on oncology. GSK will become an investor in Orchard, receiving a 19.9% equity stake.

Biogen and Ionis expand partnership

Biogen and Ionis Pharmaceuticals have expanded their strategic collaboration through a new 10-year agreement to develop novel antisense drug candidates for a broad range of neurological diseases. The collaboration capitalizes on Biogen's expertise in neuroscience research and drug development and Ionis' leadership in RNA targeted therapies with the goal of developing a broad pipeline of investigational therapies.

CROs form pediatric R&D alliance

KinderPharm LLC and Worldwide Clinical Trials Inc. have entered into a strategic alliance to deliver the world's first single center of excellence for pediatric drug development and clinical research—from inception of the initial regulatory plan to the conduct of trials on an international basis to support product registration and approval.

— Wire reports

Master Protocols in Oncology: A Review of the Landscape

Bradley Smith, Kathy Giusti, Richard Hamermesh, Dixie-Lee W. Esseltine

With technology's increasing ability to gather and analyze previously unmanageable data sets, and medicine's forays into genomics and targeted therapies, the time of the master protocol may be at hand.

PEER REVIEW

The innovative form of trial design known as a master protocol is gaining attention, particularly in oncology. "The widespread availability of next-generation genomic sequencing has opened the door to the development of precision oncology," as experts have noted.[1] With technology's increasing ability to gather and analyze previously unmanageable data sets, and medicine's forays into genomics and targeted therapies, the time of the master protocol may be at hand.

But what will it take to make the master protocol a standard in oncology research? When and under what circumstances is a master protocol appropriate and how can its use be optimized to drive patient impact?

Well-known past, ongoing, and planned master protocol studies suggested that significant progress has been made in the field establishing design and operational practices. The Harvard Business School (HBS) Kraft Precision Medicine Accelerator (referred to as "the Accelerator" throughout) saw the immense potential of the master protocol model and evidence of substantial progress. To better understand the landscape, the Accelerator brought on QuintilesIMS (now IQVIA) to conduct a review, based on primary and secondary research.

The Accelerator, with the help of QuintilesIMS, has taken on this rapidly evolving area of research—investigating past, current, and planned trials and interviewing experts from all facets of research, to understand current approaches and work with leaders to increase collaboration and patient impact across a range of cancers.

Master protocols in oncology research

Master protocols in oncology research are designed, as Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), puts it simply, "to answer more questions more efficiently and in less time."[2]

Various terms are currently used to describe study designs that differ from a traditional interventional Phase I, II, or III design, including adaptive, platform, or innovative design. Each of these terms have either specific meanings (adaptive) or are general (innovative). However, the term master protocol is well accepted to represent an ongoing trial intended for the addition or removal of drugs, arms, and study hypotheses.

Master protocols may or may not be adaptive, umbrella, or basket studies. They may be a collection of sub-studies or a complex statistical design or platform for rapid learning and decision-making. Whether umbrella, basket, or platform, a master protocol seeks to update the randomized clinical trial model for the genomic age.

Because of their ability to combine a variety of logistical, innovative, and correlative elements, while making it possible to learn more from smaller patient populations, many master protocols investigate targeted therapies, personalized medicine, and immune responses—frequently in oncology. Their ability to speed and streamline the trial process holds the promise for new, more targeted anti-cancer agents that can help more patients sooner.

The Accelerator Clinical Trials work stream

The Accelerator's Clinical Trials work stream seeks to help advance trial design across cancers by:

- Identifying best practices and sharing this knowledge across current and future trials

The Accelerator: At a Glance

The mission of the Accelerator is to speed medical breakthroughs in precision medicine. The Accelerator works by the principles of collective impact: since problems often arise from a complex combination of factors, they, therefore, can be better solved by a systemic approach to increasing collaboration and coordination among all relevant stakeholders. The principles of a common agenda, shared measurement system, mutually reinforcing activities, continuous communication, and backbone support are integral to the functioning of the Accelerator.

The Accelerator comprises four work streams. While each team holds a different focus, their separate efforts to speed cures integrate and cross-pollinate. The four work streams are as follows:

- **Direct to patient:** Amplifying the efforts of leading foundations to share best practices across patient registries, developing an understanding of the patient experience, generating data, and increasing trial enrollment through improved patient involvement.
- **Data and analytics**: Identifying solutions to use crowdsourcing, artificial intelligence, and data integration to prioritize and then answer important questions.
- **Innovative trials:** Seeking to help stakeholders improve trial design, execution, and accrual across all cancers.
- I**nvestment/venture**: Researching how philanthropy and impact investing can better foster communication.

The ultimate aim is to accelerate patients' access to new medicines and best therapies.

- Helping nonprofit organizations (NPOs) improve their understanding of design and operation of master protocols
- Working with clinical and regulatory experts to identify opportunities for speed and efficiency

The Accelerator partnered with QuintilesIMS to assess the landscape of master protocols, in order to understand and identify common challenges and best practices. This research was accomplished through interviews with external study leaders, statistical-design experts, and FDA staff, as well as literature research. Although this was a thorough effort, in practice, each of the studies continue to evolve quite rapidly. Thus, while the lessons persist in importance, the studies continue to change to meet their individual challenges and opportunities to further develop the master protocol model.

The QuintilesIMS project for the Accelerator began with an investigation into a range of master protocol trials, both ongoing and in development.

Well-known studies, started some years ago, have paved the way for a new model to conduct clinical research using master protocols: BATTLE and I-SPY 2, for lung and breast cancer, respectively, established the feasibility of a new paradigm for oncology trials, with a comprehensive approach to drugs and outcomes, supporting a collaborative research community. More recent ongoing examples include NCI-MATCH and newer trials as part of I-SPY 2.

These significantly expand the scope of a master protocol study by either greatly expanding the collaborative organization and breadth of research within a master protocol study or increasing the number of drugs, arms, and partnerships to rapidly advance clinical research.

The QuintilesIMS review of current and planned master-protocol trials included the following:

Ongoing master protocols

- I-SPY 2, a groundbreaking breast cancer study when first started in 2010 that defined the design and infrastructure of the platform study model, including a private/public partnership managed by an NPO.
- NCI-Match is an ambitious master protocol study sponsored by the National Cancer Institute (NCI) and cooperative groups to rapidly match patients to approved and novel therapies to detect promising treatments with an objective response rate greater than a predefined threshold for further research involving over 1,000 sites and 19 arms.
- Beat AML, convened by the Leukemia & Lymphoma Society and run under their LLC, for newly diagnosed elderly acute myeloid leukemia, incorporates rapid genomic screening matched to investigational therapies to develop more individualized, effective treatment approaches.
- Lung-MAP is a Phase II/III public-private collaboration with government agencies, pharma partners, and advocacy organizations, for squamous cell lung cancer, which includes biomarker-driven drug sub-studies under a single mas-

ter protocol to reduce the screen failure rate and maximize the chances of identifying successful treatments.

Master protocols in preparation/planning

- GBM AGILE, developed by the National Biomarker Development Alliance and collaborators, has built a global community and novel research platform to test new drugs in glioblastoma while maximizing the amount of information gathered from each patient in small size cohorts.
- Precision Promise, sponsored by panCAN aims to dramatically improve outcomes for pancreatic cancer patients through a transformative, patient-centric clinical trial platform that continuously and rapidly evaluates novel treatment options.
- I-SPY (2/3) continues the platform study model to confirm the efficacy of breast cancer agents that successfully graduated from the ongoing I-SPY study confirming the ability for master protocols in oncology to accelerate agents to approval.
- MyDrug is planning, under the Multiple Myeloma Research Foundation, to build on the CoMMpass registry to address multiple myeloma, profiling and targeting patients' genetic alterations, and testing sequences of therapies and novel agents to maximize patient response.

Lessons learned

From the sources analyzed and experts consulted, it is possible to identify a variety of ways in which new and future trials can be improved by learning from the challenges met by past and current trials. The QuintilesIMS study found a set of general learnings, as well as two sets of more specific challenges to be met: those related to the study design, and those related to the operating model that a master protocol uses.

General learnings

- Use of a collaborative model should be a priority—bringing together different stakeholders into one governance infrastructure improves study efficiencies.
- Neutral third parties may promote centralized processes and a strong governance structure—leadership by third-party NPOs (which can include disease foundations) can establish a governance structure and operating model as an alternative to academic-led studies.
- Groups should study the changing treatment landscape and be proactive about potential changes in treatment paradigms—statistical designs must be able to manage potential changes in standard of care or the addition or removal of study arms.
- Relevant drugs and combinations are critical—ensuring clinical relevance by an emphasis on strong hypotheses and rationale (using tools that could include crowdsourcing, competition, or AI technology to develop the best ideas for new targets and agents).

Study design

Design considerations vary, depending upon the strategic goal of the study, and result in varying levels of complexity (see Table 1).

Operating model learnings

Several operational factors can make it possible to develop an ecosystem that is collaborative while maintaining defined roles and responsibilities. Some of the critical elements that can ensure success are presented in Table 2 (see facing page).

What's ahead

Master protocol studies offer innovative potential to create a metamorphosis in oncology, offering new hope to patients and guidance to clinicians.

A Complex Picture

Study design		Considerations
Study design elements	Design flexibility	• Study should be **flexible** enough to accommodate a changing healthcare landscape, including patient quality of life and novel data resources • Design should allow for changes in standard of care after study has been initited
	Design based on sound science	• The hypothesis should be **specific and clearly defined** • Trial and trial arm duration depends on the study objectives
	Response-adaptive randomization (RAR)	• Use of RAR depends on the **study objectives**: - RAR is beneficial when the goal is to find the best treatment among several treatments and not if information on all drugs is desired
	Bayesian design	• Use of Bayesian design depends on the **study phase, objectives, and amount of available information** - Bayesian design requires availability of outcome, biomarker, or some other data to support decisions during the study - Bayesian design may be valuable when managing multiple sources of data that allow sharing the information among patient sub-groups - Bayesian designs may address uncertainties at the design stage
Study results	Timeliness	• **Adequate site selection and resourcing of staff** to drive timely results and ensure that ongoing trials provide key success metrics
	Transparency	• **CLIA labs** should be used to ensure biomarker endpoints are reproducible, and results are transparent and robust and data is shared
Input and review	External involvement	• Study design should be driven by **best idea** through competitive process • Design should include input and review from **internal and external networks**

Source: Smith et al.

Table 1. Variable study design considerations.

Through this review with QuintilesIMS and based upon its breadth of work, the Accelerator seeks to help stakeholders across all cancers collaborate and learn, with the mission of bringing better drugs to patients faster. This landscape analysis has presented several sets of common challenges to master protocol trials—particularly related to study design and operations. The hope is that considering and addressing these research challenges can improve ongoing and future trials.

Based upon its research to date, the Accelerator hopes to hone its role in improving trial design, execution, and accrual across all cancers. To this end, the Accelerator will seek all opportunities for collaboration and guidance from many experts, including those from FDA.

The Accelerator seeks to find answers to additional questions through those collaborations. Those include, but are not limited to:

- How can the master protocol model be optimized to function as a registration pathway?
- How can transparent collaboration be fostered among sponsors?
- What needs to be done to ensure that foundations can be effective, safe, and compliant IND holders?
- What needs to be done to improve/accelerate molecular patient screening—a critical element of many master protocols—as a diagnostic tool?
- How can input from various stakeholders, including regulators, best be included?

From involving stakeholders in new ways, to addressing financial concerns, to designing studies in new ways, there are a variety of ways to help the potential promise of master protocols be fulfilled. The Accelerator believes that the most powerful way to achieve this is to help participants across the healthcare industry collaborate in ever deeper and more innovative ways.

Best Practices for Success

Operating model		Best practices
Key players	Foundation	• As a neutral convener, foundations can bring together communities • Foundations may **hold the IND** but must address critical factors required for regulatory compliance • Foundations may champion the study, drive high quality results and be held accountable for its success but must leverage professional operational expertise and other operational capabilities
	Pharma	• **Multiple pharma** partners should be involved to provide their best drugs with potential for registration
	CRO	• CROs with a **flexible business model** and experienced staff to address the unique requirements of complex master protocols are needed
	Academia	• Academia and dedicated principal investigator can drive clinical research and **identify relevant research questions**, but may not be optimal partner to drive a master protocol execution
Finance	Funding strategy	• **Clear limits** on funding from each pharma partner and a defined business model will promote involvement from multiple companies
	Validated budget	• A Long-term budget and funding model should **be validated** to ensure efficient start-up and delivery of data
Study objectives	Long-term vision	• A clear end-game and objectives, including **what is next** and how results/data will be used and shared to support changes in care are required
	Clear strategy	• Study team should be able to clearly articulate the strategy including goal of study and design, and **why patients** would want to participate in the research
	Patient impact	• Study should serve as a step to **bring improvement in patient care** to ensure patients and their data are being treated ethically and wisely in clinical research
	Reach to payers and healthcare	• **Involvement with clinical practice** (payers and healthcare systems) can enable maximum impact in improvement of patient care

Source: Smith et al.

Table 2. Operating model considerations.

References

1. Redman MW, Allegra CJ. The Master Protocol Concept. *Semin Oncol.* 2015 Oct; 42(5): 724–730. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4681517/
2. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med* 2017; 377:62-70. DOI: 10.1056/NEJMra1510062. https://www.nejm.org/doi/full/10.1056/NEJMra1510062

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Maximizing Immuno-Oncology Clinical Trial Success

Luke S. Gill

Examining the unique standards and related challenges when assessing the safety and efficacy of cancer immunotherapy candidates.

PEER REVIEW

Immuno-oncology is a unique approach to cancer treatment that leverages the body's immune system to help fight cancer. Immuno-modulating agents such as interleukin-2 (IL-2) and interferon (IFN) have been used in the treatment of some solid malignancies for years, but their use has generally been limited to cancers that are immunogenic, such as melanoma and kidney cancer.

More recently, immune checkpoint inhibitors have changed the landscape of immunotherapy, and emerging therapies in cancer such as chimeric antigen receptor T-cells (CAR-T), dendritic cell vaccines, and bispecific T-cell engager (BiTE) antibodies are pushing the envelope even further.

In 2016, the cancer immunotherapy market was estimated to be $41 billion, and it is expected to grow to nearly $119 billion by 2025.[1] Small and midsized biopharmaceutical companies will play a critical role in this growth, but will need to overcome critical hurdles that are inherent in developing immunotherapeutic agents. Because immunotherapy innovations work differently than chemotherapy, they require different standards for evaluating their safety and effectiveness. Understanding these standards—and the other major challenges of immuno-oncology studies—is critical to clinical trial success.

Evaluating response to cancer immunotherapies

When evaluating oncology drugs, four distinct response patterns are generally associated with favorable overall survival:[2]

1. Response in baseline lesions

2. Stable disease with slow decline in tumor volume

3. Response following an initial increase in tumor volume

4. Response following the appearance of new lesions

Traditionally, response and efficacy with oncology agents has been measured by a set of published rules known as Response Evaluation Criteria in Solid Tumors (RECIST). However, these criteria do not easily apply to immuno-oncology agents because of the kinetics of the anti-tumor response associated with them. Unlike conventional cytotoxic therapies that may trigger rapid tumor shrinkage due to direct killing of cancer cells, immuno-oncology drugs stimulate immune cell responses that may take several months to occur. As a result, patients may exhibit an initial increase in tumor burden followed by tumor shrinkage, a phenomenon called the flare effect.

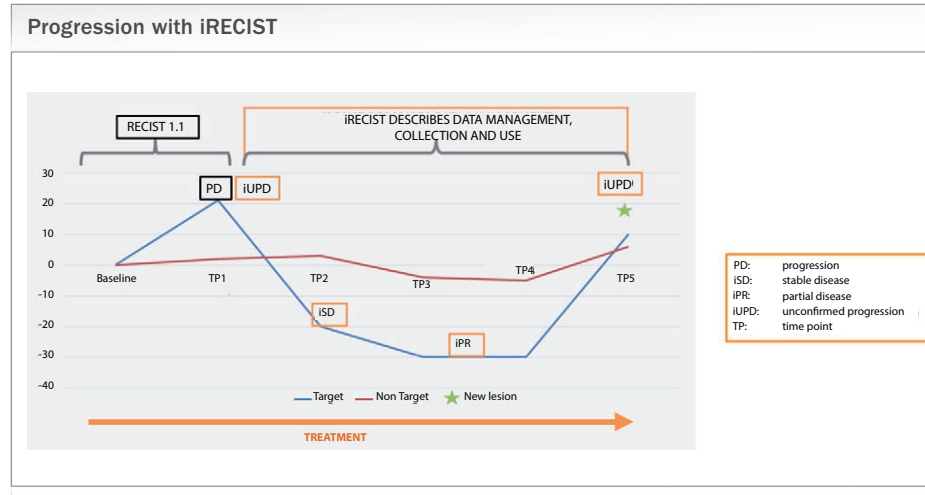
For example, ipilimumab is an anti-cytotoxic T-lymphocyte-associated antigen (CTLA)-4 antibody approved for treatment of advanced melanoma. As many as 10% of patients treated with ipilimumab who were scored with progressive disease using modified World Health Organization (WHO) criteria for tumor size were shown to achieve disease stabilization and improved overall survival.[3] Clearly, only applying RECIST criteria to immunotherapy trials can result in:

- Premature termination of therapy
- Unnecessary removal of patients from clinical trials
- Inaccurate interpretations of treatment response

A new set of rules: iRECIST

Due to the unusual pattern of treatment response associated with immuno-oncology drugs, a number of new response criteria have been developed, including immune-related response criteria (irRC), which is based on WHO criteria, and immune-related RECIST (irRECIST), which combines elements of irRC and RECIST.

In 2017, a new set of irRC was proposed by a RECIST working group comprised of members of industry, academia, the FDA, and the European Medicines Agency (EMA). This consensus guideline—called Immune RECIST (iRECIST)—standardizes and validates immune response criteria to aid in decision-making regarding continuation of therapy in clinical trials.



Source: Gill

Figure 1. Assessing tumor response using iRECIST.

iRECIST calls for the use of modified RECIST in cancer immunotherapy trials and describes a standardized approach to measuring solid tumors and defining objective change in tumor size for clinical trials.[4] iRECIST also introduces a new response criterion known as immune unconfirmed progression of disease (iUPD), which describes new overall response.

With iRECIST, the bar for progression resets if RECIST-defined progressive disease (PD) is followed at the next time point (TP) by tumor shrinkage, as seen in TP2 in Figure 1.

iRECIST has not yet been validated and should not be used as a guideline for treatment decisions. RECIST is still the gold standard for defining treatment response-based endpoints in solid tumors for pivotal registration trials. However, iRECIST can be used in conjunction with RECIST in later-phase studies, and may be used as primary response criteria in exploratory, early-phase studies.

Sponsors of cancer immunotherapy drugs who want to use iRECIST guidelines in their studies should train their operational team and communicate closely with the data and safety monitoring board (DSMB) to ensure that all stakeholders understand that these agents work differently than cytotoxic therapies.

Validating biomarkers

Current patient response rates and toxicities associated with immunotherapies have created a sense of urgency to determine which patients would most benefit from these agents. This may require companion diagnostic tests, including biomarkers and genetic sequencing data. To date, the biomarkers for immunotherapy include immunohistochemistry, flow cytometry, and next-generation sequencing, each of which has its pros and cons.

The identification of immune-specific biomarkers will help to fill knowledge gaps by providing valuable predictive and prognostic information, as well as insights on the underlying mechanisms of treatment response and resistance. This would enable development of personalized treatment plans and inform the design of combination therapies.

A major hurdle to the identification and development of clinically relevant biomarkers is the fact that immune modulation affects many cell types and involves complex interactions among the host, cancer cells, and tumor microenvironment.[5] The Society for Immunotherapy of Cancer (SITC) Biomarkers Task Force has published a series of white papers on the validation process and regulatory considerations associated with biomarkers in immunotherapy, as well as novel technologies and emerging biomarkers relevant to individualized cancer therapy.

Finding the right combination

Cancer treatment is undergoing a radical transformation in which conventional cancer drugs are being integrated with immunotherapeutic agents. For example, combined inhibition of programmed cell death 1 pathway (PD-1/PD-L1) and CTLA-4 in melanoma and non-small cell lung cancer (NSCLC) highlights the potential of combination therapies to further enhance the clinical benefits of monotherapies.

Many clinical trials are evaluating the potential synergistic effects associated with immunotherapy drug combinations. Currently, the established anti-tumor activity of PD-1/PD-L1 inhibition as monotherapy in a spectrum of cancers—coupled with its favorable toxicity profile—provides a strong rationale for its use as a backbone for combination treatments.

However, it has been shown that substantive incremental toxicity can result from immunotherapeutic combinations, depending on the patient population, dose, and schedule utilized. For example, a Phase I study combining ipilimumab with vemurafenib, a Raf inhibitor, in patients with melanoma showed significant increases in toxicity at standard dosing. This highlights the importance of flexible approaches to dose and schedule optimization. Combination therapies require not only rigorous clinical testing early in clinical development, but also the willingness to accept the use of non-standard doses or schedules of individual agents to maximize the overall risk-benefit profile.[6]

For sponsors, identifying the best candidate drug to combine or compare with an investigative agent can be challenging—and, sometimes, prohibitively expensive. Finding the right combination and comparator, at the right price, can be the difference between success and failure. In addition, sponsors should ensure that they have manufacturing resources and secure chains of custody for their candidate immunotherapies to support their clinical trials.

Identifying adverse events

Especially with the shift toward combination immunotherapy, it is becoming increasingly important for sponsors and investigators to be adept at recognizing, characterizing, and monitoring immune-related adverse events (irAEs) and other serious adverse events (SAEs).

> Training trial site staff, as well as patients, caregivers, and all members of the healthcare team on how to anticipate, recognize, and intervene on irAEs and SAEs will contribute to clinical trial success.

In general, immunotherapy agents demonstrate unique safety profiles that may differ considerable from most conventional oncology drugs. For example, treatment with checkpoint inhibitors has been associated with a variety of autoimmune-like inflammatory phenomena. Up to 23% of patients treated with ipilimumab develop SAEs, including colitis and hypophysitis.[3] When given in conjunction with dacarbazine, approximately 20% showed significant elevations of liver function tests.

Sponsors should keep in mind that toxicity does not accurately predict positive therapeutic outcome, and patients may experience irAEs or SAEs without benefiting from an anti-tumor effect. Training trial site staff, as well as patients, caregivers, and all members of the healthcare team on how to anticipate, recognize, and intervene on irAEs and SAEs will contribute to clinical trial success.

Looking to the future

Advances in our understanding of the immune response to cancer—along with recent advances in biomarker development—are increasing the number of patients with cancer who benefit from immunotherapy. As we look to the future, new immune-oncology agents and combination approaches have the potential to further expand the spectrum of patients who respond to cancer immunotherapy, improve the quality of clinical responses, and pave the way for a personalized approach to cancer treatment.

References

1. Grand View Research. Cancer Immunotherapy Market Analysis by Product, By Cancer Type and Segment Forecasts, 2014-2025. October 2017.
2. Wolchok JD, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.
3. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
4. Seymour L, et al. on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet*. 2017;18(3):e142-152.
5. Gulley JL, et al. Immunotherapy biomarkers 2016: overcoming the barriers. *J Immunother Cancer* 2017;5(29).
6. Ott PA, et al. Combination therapy: a road map. *J Immunother Cancer* 2017;5(16).

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What's Behind the Clinical Innovation Gap?

Though digital technology has improved R&D, the old generation of drugs are still considered first-choice medicines.

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I've been analyzing the discovery times of major medicines or pharma classes that still have important life-saving benefits and have changed the traditional management guidelines of diseases. The breakthrough period started with discovery of antibiotics and continued through the second part of the 20th century. Beta blockers were discovered in 1964, angiotensin-converting enzyme (ACE) inhibitors in 1971, and statins in 1980. Metformin, which is still a leading product in diabetes, was first produced in 1957. Mesalazin, the key medicine to treat inflammatory bowel diseases and Crohn's, was introduced in 1984. Bisphosphonates were synthetized in the 19th century and commercially implemented in 1960.

What can we say about this?

1. The majority of life-saving drugs that were discovered in the second part of the last century are still at the top of clinical guidelines and considered first-choice medicines.
2. Many breakthrough drugs were discovered before the advent of the biotechnological era and new, postgenomic drugs have not managed to replace them.
3. R&D in the middle of the 20th century was not so much dependent on computerized technologies and was more successful before the period of drafting the human genotype and the introduction of molecular medicine.

The last point is important. Françous Simon and Philip Kotler wrote in *Building Global Biobrands* (2009) that while biotech output surged, pharmaceutical productivity declined. A decade ago, an annual R&D spend of $15 billion produced 50 new chemical entities; the industry now spends more than $35 billion to produce 30 new compounds.

So why has postgenomic and modern biotechnological research not helped to discover breakthrough medicines similar to those of the past century? Certainly, the progress of R&D is visible in many areas of medicine. For example, the discovery of monoclonal antibodies (MABs) has dramatically improved survival for some cancer types or in the management of rheumatoid arthritis. However, the different and very expensive MABs synthetized in recent years in the fields of cardiology, diabetes, osteoporosis, Crohn's disease, or psoriasis have not been able to replace the traditional and affordable pharma products discovered 50 or 70 years earlier. Today, we have better understanding of pathophysiology of different diseases on the molecular and genetic level, but modern biotech products rarely show the advantages in terms of important clinical benefits or outcomes, in comparison with the old generation of drugs.

Does this mean that current technologies in R&D do not work? Of course not. The main weakness that I see is that R&D companies and institutions have switched from clinical orientation to more commercial- and technology-driven approaches. As a result, there are fewer people with medical backgrounds involved in preclinical research and more scientists with biotech or biochemical education now leading the molecular discovery phase.

Another issue is that we are stepping back from the classical investigative method, which places human observation, empirical data, scientific intuition, and criticism as the main categories for experimentally proven discovery. We rely too much on artificial intelligence, fight for Nobel Prizes for genomic and molecular discoveries, and place commercial interests ahead of affordable medicines that are able to dramatically prolong lives or prevent serious complications. And there is almost a stagnation in the discovery of new classes of antibiotics, which can have a global threat.

I'm confident successful biotech companies will recruit more medical scientists and specialists for the preclinical and first stages of drugs discovery. However, we should keep in mind that products like metoprolol, metformin, atorvastatin, alendronate, and lisinopril are still high points of pharma R&D, and that they were discovered mainly by practicing doctors and scientists before the implementation of digital technologies.