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The Road to True Patient Centricity

Putting patients at the center of clinical research is a continued challenge. Barriers to getting people more involved are numerous: lack of awareness, lack of health literacy and education, mistrust or desire, physician awareness or aptitude, lack of a cohesive healthcare to research pathway, lack of patient involvement in trial design, ability to find a trial, ability to adhere and stay motivated in a trial... all of these factors and more go into the overall challenge of patient centric initiatives. On the pharma R&D side, too, often the focus on patients is a transactional one, solely to improve patient recruitment, which has proved ineffective and misguided. However, many positive initiatives exist in patient centricity, and this issue, along with the March issue of Pharm Exec, touches on some of them.

Moe Alsumidaie, a contributor to Applied Clinical Trials, regularly reports about patient centricity initiatives. In his article on page 26, he summarizes the advances since he began corresponding in 2014. He notes that the FDA suggested that industry wasn’t involving the patient during the entire drug development process, and that “the industry should focus on why they are bringing drugs to market, incorporating patient diversity, and generating outcomes meaningful to patients.” FDA suspected the disconnect in patient centricity interpretations arose from C-suite level personnel within the biopharmaceutical industry.

The need to involve patient advocacy groups as a way of gaining patient insight is a growing movement and one that is shifting from a transactional, less-involved relationship to one that is more strategic. However, that too faces a holistic patient view as a challenge when within sponsor companies themselves, the patient advocacy or patient-centric function can be divided between research and commercial. As Joel Beetsch, PhD, vice president of patient advocacy at Celgene, notes in a March article in Pharmaceutical Executive, “[Manufacturers] can have two different types of patient advocacy organizations. One might be in a center of excellence within their R&D community that is really working to recruit clinical trials. Then there’s a separate function that is more associated with the business. Often, those two functions within the same company don’t communicate regularly with one another.” And while this can be common practice, Beetsch says that is not the case at Celgene, where all of those activities are in one department.

Finally, patient education and awareness is another key piece missing in clinical research. On page 18, The Center for Information and Study on Clinical Research Participation (CISCRP) offers an analysis of the evolution of its own services to the patient community as a non-profit organization. At the end of the article, the authors note, “The objectives of awareness and clinical research literacy are no longer to primarily increase patient recruitment rates. They have evolved to accommodate patient needs to influence and be a part of each patient’s healthcare and treatment decisions; build confidence and a personal sense of control in one’s own health journey; enable key stakeholders to facilitate participation; to elevate appreciation for all study volunteers; and to demonstrate the personal relevance of clinical research participation.”
## CONTENTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>The Patient Perspective on Clinical Trials</td>
</tr>
<tr>
<td>26</td>
<td>The Evolution of Patient Centricity</td>
</tr>
<tr>
<td>28</td>
<td>Portfolio Approach to Optimize Site Selection</td>
</tr>
<tr>
<td>29</td>
<td>New Models to Raise Public and Patient Awareness</td>
</tr>
<tr>
<td>29</td>
<td>The Rise of Shared Digital Health Economy and Promise of Accelerated Clinical Research</td>
</tr>
<tr>
<td>35</td>
<td>EYE ON PATIENT ADVOCACY</td>
</tr>
<tr>
<td>80</td>
<td>NEWS AND ANALYSIS</td>
</tr>
<tr>
<td>80</td>
<td>PEER REVIEWED</td>
</tr>
<tr>
<td>88</td>
<td>COMMENTARY</td>
</tr>
<tr>
<td>94</td>
<td>EDITORIAL ADVISORY BOARD</td>
</tr>
</tbody>
</table>

### Featured

#### The Patient Perspective on Clinical Trials

Lindsey Wahlstrom-Edwards, Anne-Marie Hess

Survey uncovers deeper learnings of patient perceptions of clinical research and the motivations to participate.

#### The Evolution of Patient Centricity

Moe Alsumidaie

Examining the distinct actions and advocacy that have advanced the concept from buzzword status to practical implementation in clinical studies.

#### New Models to Raise Public and Patient Awareness

Ken Getz, Ellyn Getz

Tracking the evolution and effectiveness of CISCRP's clinical research awareness and literacy campaigns.

#### Portfolio Approach to Optimize Site Selection

Vadim Paluy, MD, Vladimir Shnaydman, PhD

Optimization model evaluates the benefits of selecting a portfolio of investigative sites based on advanced analytical models.

### EYE ON PATIENT ADVOCACY

#### The Rise of Shared Digital Health Economy and Promise of Accelerated Clinical Research

Richard Tsai

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Moe Alsumidaie  
Thought Leader and Expert in the Application of Business Analytics Towards Clinical Trials and Healthcare  
New York, NY

Kiran Anancha, PhD, RPh  
Chief Operating Officer  
Honorable Health Research Institute  
Honorable Health  
Scottsdale, AZ

Townsend N. Barnett, Jr.  
Vice President, Global Head of Pre-Clinical and Clinical QA  
UCB Pharma S.A.  
Chemin du Foriest, Belgium

Kenny Blades, PhD  
Director, Global Project Management  
DOCS International  
Kent, UK

Anthony J. Costello  
Vice President, Mobile Health  
Medidata  
San Francisco, CA

Domenico Criscuolo, MD, PhD, FFPMM  
Chief Executive Officer  
Genovax  
Collereto Giacosa, Italy

Sreel Dagdai, PhD  
Specialist Leader, Life Sciences Technology Strategy  
Dezote  
Parsippany, NJ

Yakov Datsenko, MD  
Senior Clinical Research Physician  
Team Leader Immunology/Respiratory  
Boehringer Ingelheim Pharma GmbH & Co. KG  
Biberach, Germany

Edward Stewart Geary, MD  
Chief Medical Officer & Vice President  
Eisai Co., Ltd.  
Tokyo, Japan

Azhek K. Ghone, PhD  
VP, Global Services  
MakoCare  
Newark, NJ

Rahaym Gossen  
Founder  
Rebar Interactive  
New Orleans, LA

Uwe Gudat, MD  
Head of Safety, Biosimilars  
Merck Serono  
Geneva, Switzerland

Michael R. Hamrell, PhD, RAC  
President  
MORIAH Consultants  
Huntington Beach, CA

Wayne Kubick  
Chief Technology Officer  
Health Level Seven International  
Chicago, IL

Darshan Kulkarni, PharmD, Esq  
Principal Attorney  
The Kulkarni Law Firm  
Philadelphia, PA

Jeffrey Litwin, MD  
CEO  
MedAvante-ProPhase  
Princeton, NJ

Barrie Nelson  
Chief Standards Officer  
Nunocor  
Austin, TX

Vicky Parikh, MD, MPH  
Executive Director  
Mid-Atlantic Medical Research Centers  
Hollywood, MD

Prof Stephen Senn, PhD, FRSE  
Consultant Statistician  
Edinburgh, UK

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FDA CLARIFIES RESEARCH POLICIES ON CELL AND GENE THERAPIES

A surge in R&D for cutting-edge cellular and gene-based medical treatments is prompting FDA officials to spell out more specifically its plans for streamlining and modernizing plans for assessing and regulating these products. Main initiatives involve expanding the agency’s cadre of experts tasked with evaluating innovative cell and gene therapies and clarifying clinical research policies and strategies for this area.

FDA anticipates that sponsors and researchers will file more than 200 investigational new drug applications (INDs) for these products by 2020, adding to the more than 800 applications currently on file for cell-based or directly administered gene therapy applications. That pipeline will lead to the approval of 10 to 20 new drugs in this area by 2025.

Academics and research organizations are similarly enthusiastic. The MIT Focus Project, which seeks to devise new coverage and payment methods for innovative, but costly, cell and gene therapies, predicts the approval by 2030 of 40-60 important curative products in this field; these will treat about 50,000 patients and cost more than $200 billion a year.

These advances reflect a “turning point” in the development of these technologies and their application to human health, observed FDA Commissioner Scott Gottlieb and Peter Marks, director of the Center for Biologics Evaluation and Research (CBER), in a statement issued in January (see bit.ly/2FsWECP). They provide an update for the biomedical research community on agency initiatives in this area, noting similarities to the accelerated growth of antibody drugs in the late 1990s. Recent advances, they observe, have been spurred by the development of safe and effective vectors for delivering gene therapies to patients.

More expertise, advice

To continue these gains, FDA plans to add 50 reviewers to expand the expert staff in CBER and other relevant offices. The aim is to bolster the group charged with overseeing the clinical investigation, development, and review of these products. A main challenge is to recruit high-level scientists and medical officers, a continual difficulty for the agency.

Meanwhile, more FDA guidance documents aim to clarify policies and further advance innovation in this area. A recent advisory outlines how sponsors may use expedited programs to advance regenerative medicines, including the regenerative medicine advanced therapy (RMAT) designation and accelerated approval options, to facilitate the development of cellular and gene therapy products that offer meaningful improvements over available treatments for serious or life-threatening conditions. And to encourage the development of treatments in certain promising medical areas, the agency will publish guidance on developing gene therapies that target neurodegenerative disorders. Further advice will address inherited blood conditions such as hemophilia, where oversight and study requirements may vary depending on the effect of a gene therapy on a disease target. With accelerated approval approaches, FDA also will require post market follow-up studies to assess risks and possible side effects that cannot be determined prior to approval.

Minimizing study requirements

At the same time, the agency will seek to assist small firms and academic investigators that may be skirting FDA regulation for fear of being required to run costly clinical studies and to meet complex research requirements. Here, FDA plans to outline innovative trial designs that permit researchers to pool clinical data for products utilizing a common manufacturing protocol and product quality specifications.

This initiative reflects the agency’s interest in encouraging industry to adopt more modern and reliable ways to manufacture these innovative products by reassuring sponsors that additional clinical trials may not be necessary to support all changes in production processes. Guidance here will explain that in certain situations, limited bridging studies and additional real-world data may be sufficient following production changes that implement advanced technologies. At the same time, bridging studies may be needed when more than minor changes are made in manufacturing processes, a topic that will be discussed by agency and research experts at a public meeting.

While emphasizing flexibility in dealing with these innovative therapies, FDA also intends to expand enforcement actions to rein in operators that promote unregulated treatments without complying with regulatory policies. The agency is stepping up challenges to organizations and clinicians administering gene therapies without FDA oversight and approval, which thus raises the potential for compromising safety.

— Jill Wechsler

AGENCY BUDGET BOOST

After much uncertainty and delay, FDA came away with the largest boost in its annual budget in a decade as part of the final spending package approved by Congress last month. The funding package for the Department of Agriculture, which includes appropriated funds for FDA, gives the agency $3.068 billion in discretionary funding for fiscal year 2019, a $269 million increase and nearly 9% over last year’s level, noted Steven Grossman of the Alliance for a Stronger FDA.

With some $2.5 billion in approved user fees added in, FDA’s total funding level will be $5.67 billion. The legislators specified hefty expansion in funding to combat the opioid epidemic, to modernize agency data systems, and to transform digital health.

The Center for Drug Evaluation and Research (CDER) gained a $535 million budget boost. That includes $43 million to support a “new Platform for Drug Development,” including the Oncology Center for Excellence. The added resources will help create new systems for using real-world evidence to evaluate medical products, to modernize generic drug oversight, and to advance rare disease research and development.

— Jill Wechsler
EU REPORT

CUTTING BIG DATA DOWN TO SIZE IN EUROPE

In today’s era of news sharing, you can’t be too careful about what you listen to, and what you believe. And since data sources are ceaselessly multiplying, the challenge becomes all the greater in deciding how to sort through the growing floods of information, misinformation, and disinformation. Amidst all of that, how are drug developers to keep their heads above water?

This is the challenge that European health authorities are now beginning to take more seriously—as is demonstrated by a flurry of recent initiatives, and most notably by a mid-February report from the big guns of the regulators. The European Medicines Agency (EMA) and the heads of more than a dozen of Europe’s national agencies have outlined their views on how to respond to the proliferation of threats and opportunities from big data (see bit.ly/2V7v8he).

Just as a taster, the initial recommendations relating specifically to clinical trials range from the obvious to the ambitious. “Data standardization activities are critical to increase data interoperability and facilitate data sharing,” concludes the study, unremarkably. So it is necessary to agree on data formats and standards for regulatory submissions of raw patient data, via strong support to the use of global data standards, and for alignment with other regulatory bodies.

A big upgrade to the use of individual patient-level data in regulatory processes is envisioned. Direct access should be routine during review of marketing authorization applications, and authorities should have greater capacity and skills for analyzing this material and better imaging expertise, says the report. And pilot studies should be set up to define innovative outcomes from imaging data, and to determine the validity of computer-aided evaluation of images.

Still more radically, the authorities recommend systematic sharing of clinical trial data submitted for regulatory assessment. They want to see “a data-sharing culture” in Europe, in which there is full recognition of the value of clinical data sharing for drug development. “The vast majority of clinical trials are never submitted as part of a regulatory submission and standardization activities are critical to increase data interoperability and facilitate data sharing,” the report points out. So here too, it urges pilot studies to show the value of sharing of clinical data that has regulatory relevance—such as identification of safety signals, product class comparisons, and indirect comparisons of closely related medicinal products.

The report is just the first output from the joint taskforce set up by European regulators, based on the conviction that “a regulatory strategy is required to determine when and how in the product lifecycle evidence derived from such data may be acceptable for regulatory decision-making.” It offers a definition of big data, and reviews the data landscape in genomics, bioanalytical ‘omics (with a focus on proteomics), clinical trials, observational data, spontaneous adverse drug reaction (ADR) data, and social media and mHealth data. It recognizes that data may reach regulatory authorities as supportive data in the margins of more traditional analyzed structured data, or may underpin a regulatory submission as a whole. “It is thus essential that the regulatory network understands its presence and the robustness by which it was generated in order to make a competent evaluation of the submission as a whole.”

Present limitations

The current deficiencies in Europe’s capacities are catalogued. A survey of national competent authorities revealed “very limited expertise in big data analytics at national level”, “eight of 24 reported no in-house expertise in biostatistics,” and “maintaining sufficient expertise within the regulatory network will be an increasing challenge.” Concerns highlighted by industry in exploiting big data sets included data access, data integration, data validation, and data reproducibility, as well as data security and data protection.

The needs are as great beyond Europe as within Europe, the report notes. “From a regulatory perspective, global cooperation is important, as for many rare diseases and cancers or indeed rare ADRs, there may only be a handful of cases worldwide and these data need to be interoperable to derive meaningful insights.” But the particular challenges of operating across broader geographies are acknowledged, too. The report goes on to warn that “on a global level, it is important to ensure that extremely expensive and time-consuming initiatives do not pull in opposite directions but work together to achieve sustainable and global solutions.”

Similarly, there are “multiple barriers” to data-sharing in sufficient depth and detail so as to retain its utility, not least with increasingly complex data from multiple sources. Europe has a poor record in this: “Europe has failed to define a clear path to enable sustainability of many previous data-sharing efforts, particularly for observational healthcare data, and defining this should be a priority in the future,” the report states. But in addition, meeting data protection obligations on a global scale requires urgent development of global guiding principles and standards for data anonymization; it insists.

On top of that, there are more self-interested barriers: “Data sharing is additionally hindered by a reluctance to share data in order to promote individual career ambitions or protect potentially commercially valuable information,” and these demand some new mandatory elements to drive sharing.

The report takes the form of a summary of its reflections so far, published in order to gather comments and responses from stakeholders (you have until April 28 to take a look at the document and make your own views known). Meanwhile, a further group looking at cross-cutting data-processing and analytics is due to deliver a subsequent report in the first half of 2019. Early indications are that this will recommend formation of a standing advisory group to explore the applicability of big data analytic methodologies, standards, and IT architecture, so as to support the development, scientific evaluation, supervision, and monitoring of medicines. Validation of novel analytical approaches and the clinical relevance of the derived endpoints will be a key part in defining their acceptability, especially for algorithms, the European group is expected to urge.

— Peter O’Donnell
Q&A

ME, WE, AND RWE: THE IMPORTANCE OF DESIGNING FOR THE PATIENT FIRST

Real-world evidence (RWE) is a subject of increasing discussion—not to mention implementation—in clinical research, serving to supplement traditional clinical trials and offering the potential for better treatments with a faster route to market.

Perhaps less discussed is the potential for RWE to aid another emerging priority in research design: that of patient centricity, which is rapidly becoming a priority for research sponsors as well as a common call from patient advocates.

In this Q&A, the following participants offer their perspectives on the priorities, opportunities, and challenges of patient centricity in RWE collection: Helen Matthews, deputy CEO, The Cure Parkinson’s Trust—a leading UK charity to fund research to slow, stop, and reverse Parkinson’s; Jessica Morris, founder and chair, OurBrainBank, who is living with glioblastoma multiforme (GBM) (OurBrainBank is a US non-profit created by, with, and for patients with GBM to manage their disease and work to turn GBM from terminal to treatable); and Bruce Hellman, CEO and cofounder of uMotif, which offers a patient-friendly data capture platform for real-world and late-phase research.*

Q: What are the reasons for involving patients in research design?

Helen Matthews: Some preclinical researchers working on Parkinson’s-related research have never met a someone living with Parkinson’s. Involving patients means those living with the condition support study design alongside the research team, either as a sanity check or more deeply as a valued and critical friend. That’s becoming normal practice in the UK, partly because funders insist on it.

Too often patient involvement is something thought of toward the end of a process, not at its beginning. One result of not including patients early in Parkinson’s research has been a focus on movement-related issues. But non-movement issues can have a greater impact on people’s day-to-day lives: their sleep, fatigue, pain, and more. Involving patients means research is more likely to focus on things that matter most to people, delivered in a way that is relevant.

Jessica Morris: It is hard for highly aggressive, complex, and heterogenous diseases like mine to attract research funding.

Yet we can agree that the answer to the disease is likely to lie in understanding it better. Our medical research model values the objective measures of how a disease progresses, and how treatments impact—such as MRIs—over the subjective reporting from a patient, including symptoms and side effects. Patient symptom data is a largely untapped pool of information that can inform researchers, so they can better design treatments. Involving patients in that process has the added benefit of providing people with the disease to feel they are managing the disease, and not the other way round.

The OurBrainBank app empowers patients to manage their disease by tracking their symptoms and gives them hope that by donating their data we will make quicker progress to better treatments. OurBrainBank’s mission is to move GBM from terminal to treatable through the power of patients.

A major issue with rarer conditions like GBM is that drugs are often used off-label to alleviate symptoms or aspects of the condition, with little information on potential side-effects, which can become a significant problem for patients.

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Q&A

have basis to look at the value of the patient experience in research.

Q: Given RWE studies aren’t intended to replace randomized controlled trials, what are the insights we can get from patient-centric RWE studies at this relatively early stage in their use?

JM: RWE can serve as a reminder to clinicians, as well as to researchers, to consider the priorities of patients. Patients want both “complete” cures as well as better “todays.” A patient-centred approach can help to tackle this.

There are no known cures for GBM, and so patients are desperate. Patients’ idea of a cure is not always the same as clinicians. People want a cure for today, not just a traditional medical cure, but one that enhances what they can do to feel better today as they live with their condition—even including measures like diet and exercise. Eating better might not be a cure long-term but it can make you feel better today, and well-designed RWE can provide data to help improve the understanding of these sorts of outcomes—the ones that matter to patients.

One condition—clearly there are subtypes, some precisely defined, some less defined. By capturing more RWE, we can gain a better understanding of these subtypes and their respective impacts.

Bruce Hellman: RWE studies provide the opportunity for greater scale and the ability to reach large numbers of study participants in new and innovative ways. Such as through virtual or hybrid studies where participants no longer need to visit sites to take part in research.

These new forms of study can help researchers and sponsors ask different sorts of questions that haven’t been possible until now—such as investigating the link between weather and pain, or what sort of symptoms matter most to people managing long-term conditions.

Q: What do researchers need to be aware of to make sure RWE projects are considerate to patients?

HM: It’s important to remember that for progressive and degenerative diseases, what patients can do—and what is reasonable for them to do—can change over time, and daily commitments can become burdensome.

Technology can be supportive, however, identifying the right technology to use, that is not burdensome for people living with Parkinson’s, but that generates meaningful insights is key. We all need to remember that the status quo changes and we should be led by patients.

BH: To create patient-centric studies, researchers must think first and foremost about how capturing RWE can be a beneficial experience for the patient. What can we do as an industry to give patients something back in exchange for their contribution to research? How do we ensure their data is being treated with respect?

This means being considerate and reducing patient burden or reducing the perception of burden. By framing the research in a way that is valuable to the patient and makes them feel involved in the outcome of the study, patients will typically be more willing to capture and share their data for research. One way this can be done is by sharing study outputs and early findings with study participants and help them understand the impact of their contribution.

*Disclosure: The Cure Parkinson’s Trust have collaborated on uMotif’s Smart-PD trial in the NHS, and were collaborators in the “100 for Parkinson’s” open observational study. The uMotif platform powers the OurBrainBank app and public-facing observational study.

— Staff Report
Getting Serious about Plain Language Transparency

It’s time to establish standard practices to return clinical trial results summaries to patients

Ken Getz

Patients and the public are demanding higher levels of transparency and disclosure in clinical trials. And the National Institutes of Health (NIH), other government agencies, and most pharmaceutical and biotechnology companies agree that the return of plain language clinical trial results summaries is the right and ethical thing to do. But, despite broad consensus around this important issue, at the present time only 2% of all clinical trials completed or terminated within the past three years have returned their results—in plain language—to their respective study volunteers.

There are a number of perceived barriers preventing most companies from pilot ing and/or establishing processes to return plain language summaries. Most of these barriers have already been addressed, however. Regulatory pressure mandating the return of plain language summaries is also intensifying. It is clear that government and industry research sponsors alike will place greater urgency and effort into establishing and standardizing plain language results communication practices over the next 18 months.

Five primary barriers

Articles in the peer-review and trade press—and anecdotal conversations that I’ve had with clinical teams, medical writers, and disclosure personnel through my involvement at the Center for Information on Clinical Research Participation (CISCRP)—highlight five perceived barriers to adopting plain language summary disclosure programs. They are:

1. Uncertainty around resource requirements necessary to support plain language summary programs.
2. Uncertainty about the cost to implement a plain language summary program.
3. Uncertainty about how to best reach patients with relevant and useful summary information.
4. Fear of liability from disclosing competitively sensitive and promotional summary information.
5. Low perceived incentive—positive or negative—compelling compliance.

These barriers have largely been addressed by research sponsors who are already voluntarily returning their clinical trial results summaries to patients. During the past eight years, CISCRP has worked with most of these commercial and non-commercial research sponsors to develop templates, operating processes, and standard practices. Frameworks and guidelines from organizations including TransCelerate, Clinical Trials Transformation Initiative (CTTI), and Multi-Regional Clinical Trials (MRCT) Center have also been created to help sponsors navigate uncertainty and establish practices.

Research sponsors have found, for example, that medical writing and disclosure functions can share resources and personnel to support plain language summary projects. Staffing depends on the volume of clinical trial activity in the portfolio. A few research sponsors have established capability in-house to create plain language summaries, while others are outsourcing this responsibility to contract services vendors. Performing this activity internally or under contract with for-profit medical writing services may be problematic, though. These relationships can be unduly influenced by the research sponsor’s unintentional, or intentional, efforts to publish plain language summaries containing biased or promotional information. This is especially true of for-profit medical writing providers with well-established, longstanding preferred provider agreements.

Implementation costs are relatively low and most sponsors are generally able to locate funds for pilot programs. But, due to delayed efforts for establishing which function will own the activity, continuity in funding for ongoing efforts is limited. Costs are highly dependent on the size and scope of each clinical trial and the number of translations (e.g., number of global investigative sites, number of study volunteers). With respect to the latter, typically research sponsors match the languages used in the informed consent form with those in plain language summaries. Once a plain language clinical trials results communication program has been established and begins to scale, however, process efficiencies help to lower the overall cost per program.

Production and distribution costs have also been raised as concerns. Plain language summaries are typically returned to study volunteers through the investigative site; study staff send printed reports using mail-ready envelopes. A few research sponsors have been testing the distribution of digital formats, including pdf, simple data files, and html, through online portals. However, some sponsors are concerned about compromising the study volunteer-study staff relationship and they have been reluctant to move away from print distribution.

Ethical review committees review and approve informed consent language, which typically includes notification to study volunteers that they will be receiving the results of their clinical trial. Ethical review committees also review any communications associated with the return of summaries provided to study volunteers while the clinical trial is underway (e.g., reminders and “Thank You” notes).

To avoid the risk of bias and promotional summary language, and to ensure that patient and public needs are met, CISCRP (an independent non-profit) convenes an objective and neutral editorial panel of patients, patient advocates, medical professionals, and consumer health communication experts. This is done for every new plain language summary.

Following receipt of the plain language summary report, most patients choose to review it with their primary or specialty care physician. It is rare that investigative site personnel are contacted to review the summary report one or more years after the clinical trial has ended. In those instances when site staff are consulted, reported time commitments average 30 minutes or less.

Regulatory issues and return on engagement

The ethical obligation to return clinical trial results summaries to patients in “accessible” language can be traced back to the 1964...
CLINICAL TRIAL INSIGHTS

Declaration of Helsinki. Some 33 years later, in 1997, the Food and Drug Administration (FDA) Modernization Act led to the creation of a government maintained clinical trials registry (www.clinicaltrials.gov) for listing later-stage interventional studies for serious and life-threatening illnesses. Then, in 2007, the FDA Amendments Act (FDAAA) mandated that later-stage efficacy studies and approved products report clinical trial results within one year after the completion of data collection or study termination for later-stage efficacy studies and for approved products. The law also established a provisional monetary penalty of $10,000 per day (for industry-funded studies) and the loss of grant support (for NIH-funded studies) for failing to comply.

In 2010, Congress signed the Plain Writing Act into law requiring federal agencies, including the NIH, to provide all communications to the public in plain, understandable language.

In 2017 the FDA Amendment Act Title VII Final Rule was issued to clarify the registration process and regulatory requirement for submitting clinical trial results information, to expand the definition of applicable experimental treatments falling under the mandate, and to require plain language communication of information contained in the informed consent document.

The European Commission established the European Clinical Trials Database (EUDRACT) in 2001. Eleven years later, the Commission issued Eudralex Volume 10 Guideline 2012/C 302/03, which required technical results summaries for all clinical trials conducted by at least one European member state to be posted on the EUDRACT databank (https://eudract.ema.europa.eu/) within one year after completion.

In 2014 the European Commission issued Regulation 536/2014, reinforced by the European Medicines Agency’s (EMA) Regulation 007, to clarify the posting process on a new platform (EU Clinical Trials Register), expand the definition of trials to be registered, and to require that summaries be written in lay or plain language. This most recent regulation is expected to go into effect toward the end of 2019 or in early 2020.

With respect to return on engagement initiatives, several published studies suggest that higher levels of patient engagement are achieved when study volunteers receive plain language clinical trial summaries. A 2018 Tufts Center for the Study of Drug Development (CSDD)—Drug Information Association (DIA) study found that the return of plain language summaries is among a small set of patient engagement initiatives that reflect poorly on the enterprise as a whole, harm efforts to engage patients as partners in the clinical research process, and raise public and patient concern and mistrust in the research professional community.

A growing number of commercial and non-commercial sponsors will increase their efforts to return plain language results in anticipation and preparation of mandates and their enforcement.

Low levels of support and adoption reflect poorly on the clinical research enterprise as a whole, harm efforts to engage patients as partners in the process, and raise public and patient concern and mistrust.

offer a measurable return on investment due to their relatively low cost and positive impact on study volunteer experience and retention rates. And a 2017 study by CTTI, with support from Tufts CSDD, found that improvements in recruitment and retention due to patient engagement initiatives, including the return of plain language results summaries, significantly increased the expected net present value of a clinical program.

In a global survey among more than 12,000 patients, CISCPR found that the promise to return a general clinical trial results summary is among the top five most important factors influencing a study volunteer’s decision to participate. And among 2,194 clinical trial volunteers who had completed their participation, the return of plain language results summaries had a positive, statistically significant impact on their perceptions, experiences, and overall satisfaction.

Gearing up for implementation

Although research sponsors are piloting initiatives and a small number are implementing broader programs, the ethical obligation to return plain language clinical trial results summaries to study volunteers is not embraced by the clinical research enterprise. Overall low levels of support and adoption reflect poorly on the enterprise as a whole, harm efforts to engage patients as partners in the clinical research process, and raise public and patient concern and mistrust in the research professional community.

A growing number of commercial and non-commercial sponsors will increase their efforts to return plain language results in anticipation and preparation of mandates and their enforcement.

Regulation requiring government agency support is already in place but requires harder deadlines and incentives to facilitate more rapid adoption. EU and North American regulation of pharmaceutical and biotechnology companies is tightening and enforcement may become more commonplace. Industry reputation is also tenuous in the current political environment made worse recently by widespread price increases of marketed drugs.

It is in the clinical research enterprise’s best interest to support initiatives that strengthen its relationships with patient communities and the public. The return of plain language summaries reassures patients that sponsors intend to be fully transparent, regardless of the study outcome, and is an important way to demonstrate a commitment to these valuable and highly valued partnerships.

— Ken Getz, MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCPR, both based in Boston, MA. email: kenneth.getz@tufts.edu
SYSTEMIZED CLINICAL RESEARCH: ASSESSING THE BENEFITS FOR TRIAL PARTICIPANTS

“It’s obvious, but it’s not center-stage,” says Ingrid Klingmann, chair of the the European Forum for Good Clinical Practice (EFGCP). “Clinical trials do not always benefit all the patients participating in the research, despite all the injunctions of the Declaration of Helsinki and GCP.”

Klingmann points to the risks run by patients exposed to non-optimal treatment in a trial, or enrolled in trials that are poorly designed and managed, conducted against an unsuitable comparator, or never completed.

Society has more than 50 years experience of systematized clinical research, and it is time to ask whether it is working well enough for trial participants, she told Applied Clinical Trials in an interview in Brussels mid-January. Trials are of course mandatory for demonstrating the efficacy and efficiency of a treatment, and there is a political obligation to enable faster patient access to more and better treatments, she recognizes. “But are we doing trials in the right way from the point of view of participants? We should never forget that patients entering into the unknown are taking a risk—and there is something heroic about that. We have an ethical obligation to keep these heroes at the center of all these efforts.”

Klingmann reels off a long list of possibilities she sees as just crying out to be exploited across the wide range of clinical research stakeholders—all of them holding out chances of giving trial participants a better deal. One area of promise she identifies is a more adventurous exploration of how to meet regulators’ needs for demonstrations of efficacy and safety. Evidence-based decision-making demands data, and clinical trials deliver a lot of data—but is the best use being made of all that data? she muses. Recently increased openness among some regulators to consider conditional authorizations or adaptive pathways is welcome, but clarity is seriously lacking about the wider use and acceptance of new approaches.

Many of the outstanding questions about the use of real-world evidence, for instance, demand urgent answers to make sure that patient experience—good and bad—is fed into the choice and use of medicines. More determined efforts should be made to leverage patients’ often hard-won, real-life exposure into valuable insights, through greater data standardization and interoperability, linking registries, or agreeing guidelines on use of placebo or comparator. And there is a world of virtual possibilities still to be explored effectively, Klingmann says, citing moves to develop a global regulatory acceptability framework and prototypes for simulation and extrapolation through artificial intelligence, as already applied in imaging to improve diagnosis.

Klingmann sees many instances where industry could also refocus its approach to give greater priority to the interests of trial participants. Over and above its evident moral obligation to reduce harm to patients, industry could do itself a favor by going the extra mile to make a reality out of rhetorical claims to “patient-centered” development, at the same time improving their frequently uneven public image.

The realms of academia also hold real potential for improvement, she argues. Current academic clinical research projects are not reliably optimal, Klingmann considers, citing recent claims that about half the studies initiated are never reported—sometimes because they are not completed, sometimes because sponsors are reluctant to publish, sometimes because journals are unwilling to accept results, and sometimes because the studies are so poorly designed that the results are not interpretable. Clinical trial methodology merits development as a medical discipline to ensure that only experts recognized in that discipline are entitled to take responsibility for a clinical trial. “It is unacceptable for participating patients to be sub-optimally protected or involved wastefully,” Klingmann insists.

Reaching physicians

Also high among her priorities are the physicians who are actually treating patients. These represent in her view a massively underused resource. Most practicing physicians are currently unwilling to engage in trials, partly because of limited trust in a collaboration with the pharmaceutical or medical device industries. This is compounded by a politically supported reluctance to expose patients to the risk of treatment options still not evidence-based. In addition, clinical research does not enjoy a favorable reputation among much of the medical community, and the low level of engagement is due in part to a lack of understanding, with clinical research still conspicuously absent from the curricula of medical schools and post-graduate education.

Changing that perception could bring benefits to patients as well as to research. At its best, participation in trials is good for patients: if there is no treatment alternative, patients get a chance of access to a first treatment option; and in indications where treatments are available, they get more tests, they are more frequently seen and more closely monitored, and—as increasingly reported in life-threatening disease area—the enjoy better survival. In addition, widening the net of investigators would ease the chronic challenge of adequate recruitment, and at the same time would widen perspectives by avoiding the current re-use of the same pool of investigators.

Patient gaps remain

Patients too are themselves an under-exploited resource. There is a patient community that is increasingly informed, and that wishes to contribute expertise in everything from defining research priorities to study design and study conditions, but there is still no adequate infrastructure for their systematic engagement. And it is still the case that very few patients are aware of their options to impact the development of better drugs for their disease. Clinical research remains too susceptible to emotional discussion, and greater objectivity would allow a more mature relationship between public and research.

“While there is growing concern that 95% of new medicines come from industry, the funding of clinical research still depends predominantly on the private sector because society has decided not to risk public investment into new treatments.” Without a change in funding arrangements, that situation cannot change, Klingmann remarks.

— Peter O’Donnell
TOP 3 SOCIAL MEDIA

1. The Ghost of Clinical Trials Past, Present, and Future
http://bit.ly/2To4XGQ

2. Data Dilemmas in Clinical Trials Continue
http://bit.ly/2TfpvNn

3. The Impact of AI, Precision Medicine, Mobile Health Technology on Streamlined Clinical Trials

eLEARNING:
This webcast discusses the use of Signals Medical Review to improve the processes of medical monitors and enable their ability to find safety signals quicker. It also includes the latest innovations, with a demo to experience real-world medical data review through adverse event and laboratory values presented in use cases.

Learn about applying real-world evidence to rare disease drug development in this eBook. It discusses how research approaches and real-world evidence help put drugs to treat rare diseases in patients’ hands faster.

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EUROPE MAKING INROADS IN RARE DISEASE RESEARCH

Gradually—ever so gradually—Europe is getting its act together on rare disease research. It marked international rare disease day on Feb. 28 with the launch of yet one more attempt to maximize the potential of the scattered data that, if brought together, might help improve diagnosis and treatment of Europe’s 30 million rare disease patients.

An online knowledge-sharing platform on rare diseases will bring together some of the fragmented patient data accumulated across Europe in some 600 registers.

It will also—and crucially—help boost the development of standards for data collection and exchange, to overcome one of the conspicuous weaknesses to date.

The platform comprises a European Directory of Registries, a Central Metadata Repository that permits semantic interoperability between registries, and a data protection tool that will provide distinct pseudonyms for patients in different contexts, prevent duplicate registration of patients, keep a protected link between the different pseudonyms, and preserve the possibility for re-identification by a trusted third party.

Europe’s deficiencies in data management have long been evident, and its attempts to fill those gaps are still painfully slow-moving. Part of the problem is the lack of uniform development of the digital infrastructure on which data exchange depends. The progress has been so limited until now that the EU flagged up with pride what it considered a breakthrough earlier this year when e-prescriptions and some limited electronic health record information could, for the first time, be exchanged cross-border. But the advance related only to a handful of countries, and wider adoption of even this minor step is still months—even years—ahead.

As is so often the case, the underlying problem is the diversity that characterizes Europe, with 28 member states (perhaps for a limited season only—count again on March 29) with wide differences in everything from levels of prosperity to cultural traditions. In healthcare, the differences remain stark—which is why the rare diseases platform is worth more than its meager achievement might suggest.

Currently, rare disease data is not collected EU-wide and there are no common standards to analyze the information that is available, so data are often not shared among registries or across countries. Most rare disease registries in the EU are managed by individual hospitals, research institutions, pharmaceutical companies, or patient advocacy groups, and the type of data collected varies widely, from developing medicines for particular diseases to tracking instances of rare diseases over time.

This dysfunctional situation is why Europe’s health commissioner, Vytenis Andriukaitis, could legitimately boast that the platform is a genuine advance. As he pointed out, it will “address the fragmentation of data on rare diseases, promote the interoperability of existing registries and help to create new ones.”

He added—with equal justice—that the platform will also be useful for the work of the European Reference Networks, the EU’s recent attempt to create a score of centers of excellence on certain rare and complex diseases, bringing together scattered expertise. The concept is excellent. The fact that it is an innovative approach for Europe just demonstrates how late the EU’s member states have been to recognize the merits of cooperation in tackling common challenges.

Tibor Navracsics, the commissioner responsible for managing the new platform, also pointed out how the platform “will help scientists, policymakers, and patients to make the best use of data on rare diseases that, until now, have remained largely unexploited.”

“By setting EU standards for data collection and exchange, the platform will also make it easier to compare information collected in the future across Europe,” he went on. “It is a genuinely new approach. As a first step, it is good enough. But it’s a step that should have been taken long ago. Will Europe be able to catch up with international competition in this field as long as it still suffers from an Achilles heel?”

— Peter O’Donnell
REGULATORY

FDA POLICIES SUPPORT SHIFT TO DECENTRALIZED CLINICAL TRIALS

A notable benefit of using wearable devices and other innovative technology to collect patient data in real-time is to encourage the design and implementation of clinical trials conducted at the point of care. Such approaches can help biomedical research “become more agile and efficient” and reduce the cost of developing important new therapies, FDA Commissioner Scott Gottlieb said in a January policy speech designed to expand discussion and debate over how real world data (RWD) and real world evidence (RWE) can be utilized to support a range of drug development goals.

Decentralized, or virtual, or patient-centric clinical trials would facilitate recruiting, enrolling, and retaining participants in clinical studies, a major challenge and cost for study sponsors. Such approaches promise to reduce administrative burdens on sponsors and investigators, while also permitting patients to receive treatments from community providers without compromising the quality of the study or the integrity of data. The clinical research community is looking at wearables, tele-health visits, online patient diaries, e-informed consent programs, patient apps, and other tools that are easy to use and monitor, as well as reliable. Studies utilizing such innovations would also gain access to expanded sources of evidence from lab tests, insurance claims, and even media reports.

In addition to streamlining clinical research, greater use of RWD and RWE would continue to facilitate changes to product labeling by gathering evidence for adding or modifying indications to approved medicines. These approaches, moreover, could reduce the need for post-approval safety studies, which are often difficult to enroll and carry out. RWD may support more effective new dosing regimens and help develop and validate new surrogate endpoints or digital biomarkers to guide more efficient development programs. Expanded acceptance of RWE from registries, natural history studies, and chart reviews may help sponsors establish comparison arms in studies evaluating efficacy in new products, an important strategy for single arm trials in oncology and rare diseases affecting few patients.

Moving forward in this area involves the “seamless integration” of digital technology in clinical trials, Gottlieb pointed out, to help “bring clinical trials to the patient.” This involves moving prospective data collection “outside the brick and mortar boundaries of traditional clinical research facilities,” instead of always requiring patients to travel to investigator sites. More accessible, decentralized clinical trials, moreover, would permit enrollment of more diverse patient populations within community settings, which would generate information more representative of the real world to support more informed treatment decisions.

—Jill Wectshler

DEALMAKING

ROCHE TO AcQUIRE SPARK THERAPEUTICS

Roche and Spark Therapeutics, Inc. entered into a definitive merger agreement last month for Roche to fully acquire Spark Therapeutics at a price of $114.50 per share in an all-cash transaction. This corresponds to a total transaction value of approximately $4.3 billion on a fully diluted basis. This price represents a premium of approximately 122% to Spark Therapeutics’ closing price on Feb. 22, 2019, and a premium of about 19% to Spark Therapeutics’ 52-week high share price on July 9, 2018. The merger agreement has been unanimously approved by the boards of Spark Therapeutics and Roche.

Spark, based in Philadelphia, PA, is a fully integrated, commercial company committed to discovering, developing, and delivering gene therapies for genetic diseases, including blindness, hemophilia, lysosomal storage disorders, and neurodegenerative diseases.

Spark’s lead clinical asset is SPK-8011, a novel gene therapy for the treatment of hemophilia A, which is expected to start Phase III trials this year. Spark also has SPK-8016 in a Phase I/II trial aimed at addressing the hemophilia A inhibitor population. Additionally, Spark was the first company to receive FDA approval for a gene therapy for a genetic disease in 2017. Luxturna (vetretigen neapavroc-rzyl), a one-time gene therapy product indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, is currently marketed in the U.S. by Spark. The European Commission granted marketing authorization for Luxturna in 2018.

Spark’s additional clinical assets include SPK-9001, an investigational gene therapy for the potential treatment of hemophilia B in Phase II; and SPK-7001 for choroideremia in Phase I/II. The company is also developing SPK-3006 for Pompe disease and SPK-1001 for CLN2 disease (a form of Batten disease), which are expected to be ready for clinical development this year, as well as additional preclinical programs for Huntington’s disease and Stargardt disease.

Commenting on the transaction, Severin Schwan, CEO of Roche, said, “Spark Therapeutics’ proven expertise in the entire gene therapy value chain may offer important new opportunities for the treatment of serious diseases. In particular, Spark Therapeutics’ hemophilia A program could become a new therapeutic option for people living with this disease. We are also excited to continue the investments in Spark Therapeutics’ broad product portfolio and commitment to Philadelphia as a center of excellence.”

Spark will continue its operations in Philadelphia as an independent company within the Roche Group.

— Wire Report
**ALZHEIMER’S DISEASE DRUG FAILURES PLAGUE R&D IN NEUROLOGY**

Despite 2018’s successes in the neurology market, R&D setbacks in the field of Alzheimer’s disease continue to disappoint, says GlobalData, a data and analytics company.

The Alzheimer’s disease market received major blows when several amyloid targeting b-secretase (BACE) inhibitors dropped out of clinical trials during the year, including ones developed by Merck & Co., J&J, and Eli Lilly/ AstraZeneca. Maura Musciacco, director of Alzheimer’s disease (erenumab) secured the first-to-market position, whether Alzheimer’s patients will ever see a treatment of fibrodysplasia ossificans progressiva, multiple osteochondromas, and other diseases.

Under the terms of the agreement, Ipsen will pay $25.00 per share in cash upfront on completion of the transaction, for an initial aggregate consideration of $1.04 billion, plus deferred payments on the achievement of a future regulatory milestone in the form of a contingent value right (CVR) of $6.00 per share upon FDA acceptance of the new drug application (NDA) filing for palovarotene for the treatment of MO, representing an additional potential payment of $263 million. The initial cash consideration represents a premium of 77% to Clementia’s 30-day volume-weighted average stock price.

**Pharmacotherapy R&D Institute established**

Tabula Rasa HealthCare, Inc. (TRHC), a healthcare technology company advancing the field of medication safety, has launched its Scientific Precision Pharmacotherapy Research and Development Institute. The institute is based within Lake Nona Medical City in Orlando.

TRHC’s Scientific Precision Pharmacotherapy Research & Development Institute is focused on the development of proprietary products for optimizing medication regimens to improve patient outcomes, reduce utilization of healthcare services, lower healthcare costs, and manage risk. Additionally, the institute will pursue validation and recognition of these products by the scientific and regulatory communities. It will seek to establish partnerships with major academic and pharmaceutical entities in the region.

**Ipsen acquire Clementia Pharmaceuticals**

Ipsen and Clementia Pharmaceuticals have entered into an agreement for Ipsen to acquire Clementia Pharmaceuticals, including its key late-stage clinical asset, palovarotene, an investigational retinoic acid receptor gamma selective agonist for the treatment of fibrodysplasia ossificans progressiva, multiple osteochondromas, and other diseases.

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**Virtusa Partners with the IBRI**

Virtusa Corporation, a global provider of digital strategy, digital engineering, and IT outsourcing services, announced a collaboration with the Indiana Biosciences Research Institute (IBRI) to accelerate life sciences R&D. This partnership will leverage Virtusa’s vLiFE open innovation platform to enable organizations to work in a connected ecosystem that allows them to access, validate, and adopt other firms’ technologies (e.g., analytics, machine learning, artificial intelligence) and enhance the entire R&D process.

As part of this vLiFE implementation, Virtusa and the IBRI will perform comparative analyses of synthetic data with real-world data of diabetes patients to better understand how synthetic data, which is not constrained by HIPAA regulations, can accelerate research. These analyses will measure the viability of synthetic data as an alternative to real-world datasets to drive research with the IBRI’s partners.

**Maze Therapeutics launches**

Maze Therapeutics, a company focused on translating genetic insights into new medicines. The company has secured an initial investment commitment of $191 million, led by Third Rock Ventures and ARCH Venture Partners, with participation from GV, Foresite Capital, Casdin Capital, and Alexandria Venture Investments.

In recent years, the amount of genetic data has grown exponentially, leading to a better understanding of how certain mutations in genes cause disease. However, it is unclear why some people with mutations expected to cause severe disease display only mild symptoms, or—in extreme cases—are not affected at all. Maze will focus on expanding understanding of the natural disease protection provided by genetic modifiers through an integrated approach that combines studying natural human genetic variation across the globe and conducting experiments of gene perturbations.

— Wire Reports

**Charles River buys Citoxlab**

Early-stage contract research organization (CRO) Charles River Laboratories International, Inc. has signed a binding offer to acquire Citoxlab for €448 million in cash (or about $510 million based on current exchange rates), subject to customary closing adjustments. The proposed transaction is expected to close in the second quarter, subject to labor consultations, regulatory requirements, and customary closing conditions. Upon completion of the labor consultations, Citoxlab’s shareholders are expected to enter into a definitive purchase agreement.

Citoxlab is non-clinical CRO, specializing in regulated safety assessment services, non-regulated discovery services, and medical device testing. With operations in Europe and North America, the proposed acquisition of Citoxlab would further strengthen Charles River’s position by expanding its scientific portfolio and geographic footprint, which would enhance the company’s ability to partner with clients across the drug discovery and development continuum.

**Third Rock Ventures**

Third Rock Ventures last month revealed the launch of Maze Therapeutics, a company focused on translating genetic insights into new medicines. The company has secured an initial investment commitment of $191 million, led by Third Rock Ventures and ARCH Venture Partners, with participation from GV, Foresite Capital, Casdin Capital, and Alexandria Venture Investments.

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— Wire Reports
Developing an Effective Multimodal Recruitment Plan

A case study of a Parkinson’s disease trial demonstrates how one study team met its enrollment goals

Bernadette Siddiqi

The Michael J. Fox Foundation for Parkinson’s Research (MJFF) aims to speed clinical research by removing obstacles that stand in the way of drug development. In pursuit of this mission, the Foundation gathers insights from a wide range of stakeholders and uses these perspectives to enhance clinical trial processes from start to finish. In *Applied Clinical Trials’* Eye on Patient Advocacy series, we will share best practices and lessons learned from the field of Parkinson’s research that can be applied to clinical trials across disease states. In our second column in the series, we explore how one study team implemented a multimodal recruitment strategy to meet their target enrollment six months ahead of schedule.

**Background**

STEADY-PD III was a 36-month, double-blind, randomized, placebo-controlled study of isradipine, a repurposed anti-hypertensive drug, in people with early Parkinson’s disease (PD). The projected recruitment period was 18 months at 57 academic research sites across North America.

**Methods**

Participants and procedures

STEADY-PD III aimed to enroll 336 men and women with early-stage idiopathic PD. Participants had to be older than 30 at the time of diagnosis, diagnosed less than three years prior, and not receiving PD symptomatic therapy (e.g., levodopa, dopamine agonist or MAO-B inhibitor) or projected to require symptomatic therapy for at least three months from baseline visit. To participate in the study, eligible participants agreed to be followed for up to 36 months and complete 12 in-person visits and four telephone visits. The projected recruitment period of 18 months was based on previously completed studies that targeted a similar PD population.

**Forming a recruitment committee**

Early in the planning process, the STEADY-PD III team identified and engaged key stakeholders from across the recruitment landscape to provide input on constituent motivations, knowledge gaps, and outreach methods. This group, the recruitment committee, consisted of:

- STEADY-PD III principal investigators
- Site representatives (investigator and/or coordinator)
- A representative from The Michael J. Fox Foundation (MJFF)
- A representative from the National Institute of Neurological Disorders and Stroke (NINDS)
- Patient advocates

The recruitment committee consulted with other national PD organizations, including the National Parkinson Foundation (NPF) and the Parkinson Disease Foundation (PDF), which have since merged to form the Parkinson’s Foundation.

With this guidance, the committee developed a multimodal recruitment strategy aimed at educating individuals in the PD community about STEADY-PD III and increasing awareness of resources related to the trial. This strategy was implemented through 1) in-person meetings and events with community groups, physician networks, and support groups; and 2) development of a heightened online presence using mixed media outlets. MJFF’s Recruitment and Retention Toolkit materials (accessible at michaeljfox.org/resourcepack), such as a “Physician Referral Letter” and a “Patient-Facing Slide Deck,” facilitated outreach efforts, as did grassroots patient engagement through patient organizations.

A greater online presence was cultivated through 1) creation of a study-specific website (steadypd3.com); 2) press releases (templates were provided to sites) posted to websites such as NINDS; 3) use of Fox Trial Finder—MJFF’s online trial matching service that enables the Parkinson’s community to connect with trial teams (foxtrial-
finder.org); and 4) webinars and podcasts hosted by the STEADY-PD III study principal investigators and broadcast to the networks of patient organizations. Throughout the enrollment period, the recruitment committee met monthly to review recruitment strategies, monitor enrollment at the study and site level, and identify challenges and solutions to any recruitment issues.

Results
A study enrollment report (see Figure 1 on facing page), generated after all participants had been recruited, shows a steeper slope of actual vs. anticipated enrollment, reflecting a recruitment period accelerated by six months. In addition, the pre-specified goal of 10% minority recruitment was met. Analysis of MJFF communications that took place prior to and throughout the recruitment period provides insight into the role of mixed media in generating awareness of the trial and directing individuals to resources for learning more about participation. In March 2014, MJFF, with study leadership, released a podcast that reported iridapine was moving to Phase III testing, and recruitment would begin later that same year. The podcast was downloaded by 2,043 iTunes listeners. This was followed by an uptick in traffic to the STEADY-PD III website that began in May 2014 and peaked in July 2014 (see Figure 2). One of the steepest peaks occurred in January 2015, after a December 2014 MJFF webinar that focused on therapies with the potential to slow or stop Parkinson’s progression and highlighted the STEADY-PD III trial. A third peak took place in November 2015, after an October 2015 MJFF webinar and podcast on studies to slow or stop PD.

A multitude of subject referral sources bolstered STEADY-PD III recruitment success (see Figure 3). Referral sources were recorded at the time of screening and logged into case report forms. These data indicate the top four referral sources were site personnel (53%); neurologists (24%); Fox Trial Finder (10.2%); and MJFF communications (3.9%).

Discussion
By having a comprehensive recruitment plan and involving key stakeholders early in the planning phase of the clinical trial, STEADY-PD III was able to successfully recruit its full target population six months ahead of schedule. They identified study- and site-level barriers that had the potential to negatively impact recruitment, and were able to develop a strategy to mitigate them. One important component of that strategy was implementation of a comprehensive outreach and awareness campaign. Patient engagement via advocacy organizations; local events including the Brain and Health Fair and the annual Parkinson’s Unity Walk; the power of digital media through webinars and press releases; technology such as Fox Trial Finder to connect volunteers to trial teams; and increased participation of historically underrepresented minority populations with community engagement, translation of materials, and outreach through local publications such as the “Southwestern Parkinson’s Newsletter.” The use of local grassroots events and digital media activities, combined with a proactive approach to recruitment, helped to engage and make aware a broader population than would have been possible for clinical trial sites alone. This approach also enabled study teams to connect with a more diverse population of patients who obtained their information from a variety of media and news sources. While the impact of these efforts is somewhat challenged by self-reported referral source data (see Figure 3), we posit that this is less about the efficacy of these efforts and more about challenges stemming from memory recall bias in referral source attribution. Greater efforts such as interviewer training, better referral source definition, and alternative means of data collection should be considered for future recruitment campaigns to improve the accuracy of attribution.

Bernadette Siddiqi, MA, is an Associate Director on the Recruitment and Retention team at The Michael J. Fox Foundation for Parkinson’s Research. To contact the MJFF Recruitment and Retention Team, email: trialsupport@michaeljfox.org.

MJFF would like to acknowledge the following individuals for their contribution to the research presented in this case study: Sarah Berk, MPH; Kevin Biglan, MD, MPH; Brittany L. Greco; Robert G. Holloway, MD, MPH; Catherine M. Kopil, PhD; Claire Meunier, MBA; and Tanya Simuni, MD

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New Models to Raise Public and Patient Awareness

Ken Getz, Ellyn Getz

Tracking the evolution and effectiveness of CISCRP’s clinical research awareness and literacy campaigns.

Mass media coverage and popular cultural depictions of clinical research during the past decade have continued to grow. For the vast majority of the public, these channels are the dominant educational medium, becoming even more so with the rapid influx of programming and content that can be easily accessed and streamed over the internet and shared on social media. Most of this exposure—unfortunately—has been negative and/or unbalanced, focusing largely on risks, human error, and questionable motives.

During that same timeframe, new and expanded programs and initiatives designed to raise public awareness and improve clinical research literacy—particularly among minority and underserved communities—have been implemented. This article looks at the current environment for public and patient awareness and education and discusses changes that the Center for Information and Study on Clinical Research (CISCRP) and others are making to be more effective. These approaches have refined the focus of educational content and have better leveraged the reach and frequency of these outreach and communication channels. CISCRP’s novel programs are having an impact, and they are evolving and expanding to counteract the effects of wide-spread negative and unbalanced exposure.

A powerful communication channel

Broad reach, high frequency, and the integration of communication formats have reinforced and expanded the impact of news, entertainment, and social networks, but coverage is typically superficial, uninformed, and sensationalized. News media, for example, has no shortage of clinical research-related topics to write about, but news bureaus operate with leaner editorial staff today and rely increasingly on freelancers. And most journalists have little to no prior knowledge about clinical research and must hastily gather information and interview quotes while facing tight deadlines and editorial demands for headline-grabbing coverage. As a result, although some articles profile patients and families that have found hope in clinical trials and investigational treatments, the majority provide a negative and often sensationalistic focus on mistakes made by clinical research professionals, concealment, fraud, and corruption.

Given their expansive scope, the full reach of these channels is difficult to gauge. To assess frequency and positioning, CISCRP reviewed a convenience sample of content that appeared in newspapers and in film to assess how clinical research is depicted over time. We compiled and evaluated articles focusing specifically on patient experiences in clinical trials that appeared in three major national newspapers—USA Today, The New York Times, and The Wall Street Journal—between 2016 and 2018. The results of this assessment were compared with a similar approach conducted 15 years ago at CISCRP’s inception. We did not count the educational supplements that CISCRP has been recently producing and distributing through USA Today.

We observed a 27% increase in the number of articles that appeared in these major newspapers—33 that appeared in the 2001–2003 timeframe and 42 in the 2016–2018 period. We found that the proportion of articles that offered unbalanced, negative coverage had not changed during the 15-year time horizon. In the earlier period, 59% of the articles were negative; 60% of the articles were negative in the more recent period.

Trends in fictional film and television—two popular culture mediums with extensive reach—are even more alarming. There were very few films and TV movies focusing specifically on patients in clinical research in the 2003 timeframe. The Constant Gardner, starring Ralph Fiennes and Rachel Weiss, was released in 2005, and it focused on a healthcare activist murdered before she was able to expose a large pharmaceutical company that
had been exploiting a vulnerable population of study volunteers. In 2018, we identified 10 major fictional stories in film and TV including Side Effects with Rooney Mara, Channing Tatum, and Jude Law; Dead Pool with Ryan Reynolds; and Maniac with Emma Stone and Jonah Hill. Each of these films depicts experimental treatments and procedures for severe and chronic medical conditions that have run amok. In 2017, Oprah Winfrey starred in a movie for HBO based on the best-selling book The Immortal Life of Henrietta Lacks. The film told the true story of HeLa cells, one of the most commonly used cell lines in scientific research, gathered without consent or remuneration to the patient and her family.

Although it is not their primary objective, the star power and story lines in these movies arguably reach and influence the largest audiences. All but one of these fictional movies provided any information that might help educate and inform patients with diverse medical conditions about clinical research and the participation process.

There is a silver lining. Most coverage in the mass media and in popular culture—including film and literature—is removed from and lacks personal relevance to a large percentage of its audience. The themes and messages are not tailored or targeted. They are unable to address the highly personalized nature of each person’s health, medical journey, and learning style enhanced by interactions with trusted advisors in individualized locations and communications.

Coverage in the news and in entertainment media is not coordinated and integrated into the many systems and stakeholders that facilitate patient engagement. Numerous studies in the literature demonstrate that clinical research participation is a team-based undertaking: patients rely on their personal healthcare providers and trusted family, friends, and professionals to make decisions and follow-through with their participation in clinical research.

CISCRP’s awareness-building and education strategy has been evolving to take advantage of these weaknesses.

**Expanded and new public and patient awareness and education models**

AWARE for All was CISCRP’s first public and patient awareness and education campaign, launched in 2003. At that time, we announced the new program in Applied Clinical Trials. It is a live event, produced in major metropolitan areas in the U.S. and to a lesser extent in Europe, that requires six to eight months of planning and awareness-building to engage patients, the public, local health and clinical research professionals, minority community centers, lay leaders, and community-based disease and patient advocacy groups. AWARE’s success depends greatly on the active participation and support of local stakeholders and the accessibility of the event to public transportation.

Since its introduction, AWARE’s format and outreach strategy have adapted to better accommodate local needs and attract diverse communities. From the outset, CISCRP has developed educational material with input from patients and the lay community to ensure that it is culturally sensitive at the grassroots level. Between 2003–2012, CISCRP hosted three events annually, typically on a Saturday as a full-day program with nine or 10 breakout workshops. Three to five free health screenings were provided at these AWARE programs. Depending on local community involvement location, each program received between 150 and 250 attendees. While audience members enjoyed extensive educational programming with an opportunity to select workshops of interest, many attendees suggested CISCRP consider a shorter program format on a weekday evening to accommodate busy weekend schedules and family time.

Since 2013, the AWARE program format has been modified to improve convenience, address time constraints, and to increase value and relevance. The programs are held on weekdays—Tuesday, Wednesday, or Thursday—typically between 5–8 pm. We have tripled the number of free health screenings. And CISCRP has increased the number of programs to include four to six cities each year.

From the outset, CISCRP has marketed and promoted AWARE through paid advertisements in local newspapers, social media, printed flyers and postcards, mailed brochures, public transit advertisements, press releases, media alerts, radio and TV public service announcements (PSAs), and community calendars. We have also developed a promotion toolkit for local community groups to use within their own outreach channels in support of their AWARE program. Much of this marketing and promotion begins months earlier to create awareness momentum building up to the actual AWARE event.

CISCRP places a disproportionately high investment of time and staff on local community-based approaches to facilitate awareness. We work with local advocacy groups or hospitals; encourage colleagues, family, friends, doctors, and research teams to extend personal invitations; and hold in-person conversations at health fairs and local events.

Over the past five years, with national sponsorship from EMD Serono and the Lupus Research Alliance, CISCRP has boosted AWARE’s online presence through digital event pages and sponsored social media posts. The number of impressions now reaches two million to four million in each AWARE city entered. Every program has seen a dramatic increase in average attendance, now attracting between 300 and 600 people with a high percentage from minority and underserved communities. After every event, the number of inquiries and searches for clinical trials on the CISCRP website increases by 30% to 40%. And as the program model has evolved, we have also seen an increase in the number of health and clinical research professionals and exhibitors at each event.
In the aggregate, since 2013, 70% of AWARE attendees have been from minority communities; 71% have never participated in a clinical trial; 20% have never heard about clinical research prior to attending or receiving information about the event; and 56% report knowing very little about clinical research in general. Post-program, 83% of AWARE participants report that they are more likely to volunteer for a clinical study (vs. 43% pre-program); 94% report an interest in participating if invited by their doctor; 96% of our attendees are likely to tell their family and friends about something they learned at our program; and 88% would consider suggesting that their family or friends participate in a trial.

Since 2016, CISCRP has been pairing its live AWARE event with novel highly interactive and personally relevant educational programs that attract more local media coverage and create buzz and excitement leading up to the local AWARE event. After hosting each of these initiatives in underserved communities in the weeks prior to the event, CISCRP has seen event pre-registrations increase by more than 50%.

In late 2016, CISCRP collaborated with Sanofi and creative ad agency Langland to produce an MT Pharmacy (bit.ly/2EIPvL4) in the heart of downtown Newark. A month prior to the AWARE for All - Newark program, we established a pharmacy with empty store shelves to demonstrate what modern medicine would look like without clinical trials and study volunteers. Pharmacy staff were recruited locally and trained to answer questions about clinical research from visitors to the store. Local coverage and buzz boosted registrations and long after the event, the MT Pharmacy’s important educational message continues to resonate on YouTube and other digital and social media channels.

CISCRP collaborated with Janssen and Wondros (another creative agency) to produce a mobile unit that traveled around the sprawling Los Angeles community in the weeks leading up to the AWARE for All – LA 2018 program (bit.ly/2EKPqIR). The customized recreational vehicle contained interactive displays with educational information about clinical research and about the upcoming AWARE program. CISCRP also trained local “ambassadors,” including local celebrities who volunteered their time to speak directly with the community, promote the event, answer questions, and refer the public to other resources. The Journey to Better Health initiative is now gaining visibility on social media channels and has recently received a SCOPE Participant Engagement award for its impact.

Creating ground cover with public service messages

During the past 15 years, CISCRP and other organizations—including the Pharmaceutical Research and Manufacturers of America (PhRMA) and TransCelerate BioPharma—have increased the frequency of public and patient awareness-building campaigns and expanded reach through digital and online channels supported by dedicated web portals containing educational resources. These initiatives have also refined their positioning to emphasize the gift of study volunteer participation, the personal relevance of clinical research, and the collective contribution of clinical research professionals.

In the early 2000s, most public service announcements focused on a specific breakthrough therapy and individual company contribution to science and innovation. Launched in 2017, the #GOBOLDLY campaign (bit.ly/2EJkusA), initiated by PhRMA on behalf of America’s biopharmaceutical companies, presents stories highlighting the bold risks that pharmaceutical and biotechnology organizations have taken to develop new treatments that improve medical conditions and public health. TransCelerate’s 2018 One Person Closer campaign (@OnePersonCloser) features stories of clinical researchers, healthcare professionals, and patients to personalize the clinical research experience and demonstrate the partnership that must exist between them. The One Person Closer campaign has been featured and discussed in past Applied Clinical Trials articles (bit.ly/2tPDS3L).

Since its founding, CISCRP has developed several PSAs. All of CISCRP’s campaigns gathered input from patients, advocacy groups, and professionals and are designed to engender appreciation for study volunteers and the importance that participation brings to developing treatments that benefit society. All PSAs are still in use, with earlier
messages primarily appearing on posters and websites in hospitals and in medical and research center offices.

CISCRP’s first PSA launched in 2004—"Behind Every Medicine are the Volunteers Who Take Part in Clinical Research Studies”—was developed in collaboration with the U.S. Department of Health and Human Services (HHS). In 2007, CISCRP launched the PSA “Medical Heroes Can Be Found in Everyday Places.” When it was introduced, Eli Lilly ran the campaign concurrently with traditional patient recruitment efforts. In separate pilots, Lilly observed a 38% increase in monthly enrollment rates when a radio Medical Heroes PSA was run concurrently and a 140% increase in monthly enrollment rates when radio and TV Medical Heroes PSAs were used. Both CISCRP programs have been written about extensively in past Applied Clinical Trials articles (bit.ly/25M1ayq).

Our most recent PSA, the “Medical Hero to Millions” campaign (see facing page), was launched in 2018 and has expanded frequency, continuity, and reach through ongoing repeat usage in social and digital media and content licensing arrangements. In partnership with USA Today, CISCRP now produces a supplement every six months with individual patient stories, educational content, messages of appreciation from pharmaceutical companies (e.g., Merck & Co., Pfizer, Biogen, TransCelerate, and Lilly) and the CISCRP PSA. Each supplement reaches more than 750,000 in its printed circulation and more than one million readers through each digital edition. The PSA has also appeared in a number of print and digital publications, including the National Basketball Association’s HOOP magazine, which reaches approximately two million people, and in Major League Baseball’s All-Star magazine, reaching an estimated 2.2 million in print and digital formats. CISCRP continues to establish opportunities to extend the reach of its Medical Hero to Millions campaign.

Looking ahead
We are learning a great deal about how to improve the effectiveness and reach of our awareness- and clinical research literacy-building initiatives. Progress and success are due to many factors, including engaging patients and the local community around highly personal and relevant positioning; establishing customized programs in the heart of individual communities; connecting national and local outreach; leveraging a wide range of communication channels with print, digital and social media formats; coordinating and integrating educational programs and resources; maintaining frequency and continuity of messages; and enabling the integral patient-professional relationships.

This year, CISCRP and Janssen Pharmaceutical Companies of Johnson & Johnson are expanding the Journey to Better Health mobile educational program to include three additional U.S. cities. CISCRP is in discussions to take the MT Pharmacy to additional inner cities in the U.S. and in Europe. CISCRP is also exploring the introduction of Clinical Research Navigators to operate within and between community centers, physician and healthcare provider communities, patients, and their families. And we are increasing the frequency and reach of our national newspaper supplements and adding a new supplement in a major European paper.

CISCRP continues to seek funding to implement its science museum initiative designed to raise awareness and overall clinical research literacy among elementary through high school-aged children. We wrote about this program in Applied Clinical Trials several years ago (bit.ly/2GWdU4j). No science museum has ever featured and recognized clinical research volunteers. CISCRP plans to develop and exhibit to occupy a 1,000 square foot area with 10 stations offering interactivity, problem-solving, and experiential learning. The museum exhibit will travel to different cities and will generate local and national media attention and support from the local clinical research community. Children and their families will move from station to station through the exhibit, where they can hear and observe real study volunteer stories and experiences and learn about the clinical research process, one’s rights as a volunteer, and the many people who have participated in clinical trials that resulted in well-known and age-relevant new treatments. Museum visitors will have a chance to send “thank you” notes and words of appreciation electronically to study volunteers that will be posted on websites and local bulletin boards.

The objectives of awareness and clinical research literacy are no longer to primarily increase patient recruitment rates. They have evolved to accommodate patient needs to influence and be a part of each patient’s healthcare and treatment decisions.

We have seen a profound evolution in our thinking about building awareness. Historically, the clinical research enterprise focused on raising the visibility of individual companies and their breakthrough innovations. The enterprise now collectively embraces the shared need to raise awareness in a personalized way while simultaneously coordinating and integrating with the many stakeholders that support patient engagement.

The objectives of awareness and clinical research literacy are no longer to primarily increase patient recruitment rates. They have evolved to accommodate patient needs to influence and be a part of each patient’s healthcare and treatment decisions; build confidence and a personal sense of control in one’s own health journey; enable key stakeholders to facilitate participations; to elevate appreciation for all study volunteers; and to demonstrate the personal relevance of clinical research participation.

Ken Getz is Founder and Board Chair, CISCRP, and an Associate Professor at Tufts Center for the Study of Drug Development (CSDDD); Elyn Getz is Senior Manager, Development and Community Engagement, CISCRP.
The Patient Perspective on Clinical Trials

Lindsey Wahlstrom-Edwards, Anne-Marie Hess

Survey uncovers deeper learnings of patient perceptions of clinical research and the motivations to participate.

For the past several years, there has been increasing discussion of what patient centricity means in clinical trials. The premise is that better study designs, approaches, and services that are focused on the needs and preferences of patients can improve clinical research participation and, therefore, help advance the development of medicine and medical devices. Yet, despite the focus on this concept, the general consensus is that much work remains to realize its potential.

Previous research by the Center for Information and Study on Clinical Research Participation (CISCRP) has shown that patients typically partake in clinical research for both altruistic reasons and with hopes of benefiting their personal health (see bit.ly/2EbZXg2). Other research has also begun to identify what patients want when participating in a trial.

While this is valuable research, the industry hasn’t addressed some important questions: Do patient needs and preferences vary by condition and other patient demographics? Could gaining a better understanding of patients’ lives and the factors that affect their decision to participate in the trial help to create a more attractive patient experience? Is it time to think about making the studies fit the patients’ needs better? What would it mean to move away from viewing patients as subjects in medical research, and engaging them as the stakeholders they are?

Overview of survey and methods

During the summer of 2018, Antidote Technologies and SCORR Marketing partnered on a survey to gain a deeper understanding of patient perceptions of clinical trials and their motivations to participate. The survey also was designed to identify differences related to condition, household income, education, ethnicity, and gender.

Survey participants were recruited to participate by Antidote’s partners: American Kidney Fund, Allergy & Asthma Network, Healthline, JDRF, Lung Cancer Alliance, Lupus Research Alliance, Melanoma Research Alliance, and Multiple Sclerosis Association of America. Each partner organization distributed the survey to its membership through a combination of emails, website posts, and social media posts. Some worked with other partner organizations in their disease area to generate responses from caregivers and patients.

About the sample

Of the nearly 4,000 survey respondents, the majority (89%) identified as a patient. Twenty-seven percent of respondents have multiple sclerosis (MS), 15% have asthma and/or allergies, 13% have kidney disease, 12% have melanoma, 12% have type 1 diabetes, 10% have lupus, 6% have lung cancer, and 5% have gastrointestinal disease. Twenty-six percent of respondents had participated in a clinical trial at the time of data collection.

Most survey respondents (84%) had at least some college or a college degree, and more than half (53%) reported an annual household income of less than $75,000. The sample skewed older (74% of respondents were over the age of 45), white (90% of respondents), and female (80%).

Patient motivators for participating in medical research

Providing prospective patients with the right information to make a decision starts with understanding what drives patients to join a trial in the first place (see Table 1 on facing page).

Of the 26% of the respondents who had previously joined a clinical trial:

- 75% reported that the major reason or one of the major reasons they joined the clinical trial was to help future patients.
Patent Engagement

- 69% said they participated to improve their quality of life.
- 63% indicated they were highly motivated to participate in order to receive the best care possible.

All survey participants rated the importance of 16 potential motivators to take part in a trial. Each motivator was placed in one of the following categories: safety concerns, health benefits, logistical concerns, institutional support, and financial benefits. The percentage of the survey population rating the type of consideration as very important and the average ordinal ranking (where a lower number indicates a higher ranking; see Table 2).

Safety

When we asked respondents about the possible motivators to participate in a clinical trial, unsurprisingly, safety topped the list of priorities. Seventy-three percent said it was very important that the research not interfere with their current treatment or make their conditions worse. This was the chief safety concern expressed. Of the eight condition categories included in the survey, patients with kidney disease assigned the highest importance to the idea that the clinical trial should do no harm.

Institutional support

Having someone available to answer questions throughout the study (66%) and their doctor’s support for their decision to participate (50%) were important to respondents as well. Lung cancer and melanoma patients were most likely to deem it “very important” that their doctor supports their decision to join a clinical trial. Women are more likely to value the importance of having their questions answered throughout the study.

Health benefits

The potential to benefit their personal health was also important to the respondents. About two-thirds (67%) of respondents identified this statement as the top health benefit: “The trial provides me with a drug, therapy, treatment, or medical device that potentially could extend or improve the quality of my life.”

Logistics

Logistics play a role in decision-making as well. Respondents felt it very important that they could complete the entire trial. More than half (59%) of the respondents deemed this as very important and the top logistical concern. Patients with kidney disease, MS, or allergy/asthma place a higher priority on logistical factors than patients with other conditions. Overall, only a minority of respondents said it is very important that a trial doesn’t take time away from their obligations and, similarly, only a minority considered it very important to have clinical researchers make home visits.

Financial benefits

Financial benefits, while very important to some, are generally

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Table 1. The influence levels of common drivers of trial participation reported by survey respondents.

<table>
<thead>
<tr>
<th>REASON</th>
<th>THIS WAS THE MAJOR REASON</th>
<th>THIS WAS ONE OF THE MAJOR REASONS</th>
<th>YES, BUT THIS WASN’T REALLY WHY</th>
<th>THIS WASN’T REALLY THE REASON BUT WAS A SMALL FACTOR</th>
<th>NO, THIS WASN’T THE REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>I wanted to help future patients who come after me.</td>
<td>34%</td>
<td>41%</td>
<td>13%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>I wanted to improve my quality of life.</td>
<td>33%</td>
<td>36%</td>
<td>12%</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>I wanted to receive the best care possible.</td>
<td>31%</td>
<td>32%</td>
<td>15%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>I wanted to receive the most up-to-date therapies without the high expense.</td>
<td>25%</td>
<td>28%</td>
<td>14%</td>
<td>9%</td>
<td>24%</td>
</tr>
<tr>
<td>I joined to extend my life.</td>
<td>20%</td>
<td>21%</td>
<td>10%</td>
<td>11%</td>
<td>38%</td>
</tr>
<tr>
<td>I was following my doctor’s recommendation.</td>
<td>13%</td>
<td>19%</td>
<td>10%</td>
<td>9%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Source: Antidote Technologies and SCORR Marketing Survey

Table 2. Respondents ranked potential motivators for trial participation by category.

Motivational Factors

<table>
<thead>
<tr>
<th>Motivator</th>
<th>AVG.% “VERY IMPORTANT”</th>
<th>AVG. ORDINAL RANKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety concerns (3)</td>
<td>63%</td>
<td>4</td>
</tr>
<tr>
<td>Institutional support (2)</td>
<td>58%</td>
<td>6</td>
</tr>
<tr>
<td>Health benefits (3)</td>
<td>54%</td>
<td>8</td>
</tr>
<tr>
<td>Logistical concerns (5)</td>
<td>45%</td>
<td>9</td>
</tr>
<tr>
<td>Financial benefits (3)</td>
<td>25%</td>
<td>14</td>
</tr>
</tbody>
</table>

Source: Antidote Technologies and SCORR Marketing Survey.
viewed as less important than other considerations. Oncology and type 1 diabetes patients were the least inclined to be concerned with financial considerations. Less than half (46%) of the respondents said being compensated to participate would be a motivator; however, younger respondents or those with lower household incomes were much more inclined to believe compensation would be a motivator to participate.

Patients as partners
A key element of patient centricity may relate to the industry’s ability to truly embrace patients as partners. And this effort revolves around medical professionals:

• 90% said that talking with doctors, clinical trial coordinators, and nurses involved in the research would either “very likely” or “likely” help them feel more like a partner in the research.
• Older patients have a stronger preference for talking with not only medical professionals, but also other patients like them or the hospital or company responsible for the project.

However, despite the influential role medical professionals have, only one-third of these respondents have ever talked about research with their doctor.

Similarly, having the necessary information to make well-informed decisions about participation is a key theme that runs through many of the patient responses:

• 77% want the industry to make it easier to learn about clinical trials.
• 70% would like information about findings from clinical trials to be more readily available.
• 66% desire clearer information about the costs that they will incur (time, financial, etc.).
• 56% want healthcare professionals (HCPs) to speak with them about clinical research before discussing participation in a specific trial.

Patient obstacles
The results of the survey raise important points about clinical research:

• Patients with life-threatening conditions are most concerned about gaining access to treatments.
• Individuals whose condition limits their mobility are concerned about logistical factors.
• People with asthma or allergies—a condition that impacts low-income people more—are concerned about the financial obstacles to participating in medical research.

More important than these findings is the confirmation that there is not a one-size-fits-all solution for engaging individuals in medical research. Rather, it is important to consider the particular obstacles facing patients when they are making decisions about whether or not to participate.

Providing information is a start. While survey respondents showed a clear preference for receiving information about clinical trials from their doctor or other HCP, 49% want to receive information from patients who have previously participated in a clinical trial (especially true for minority patients who haven’t joined a trial before), and almost twice as many preferred to receive information from an advocacy/nonprofit organization or health and wellness website (42%) than from a drug company or advertisement.

In addition to the survey findings, issues like low health literacy and the growing use of the internet for health information point to the need to better engage patient advocacy groups and medical professionals not only in recruiting participants for clinical trials, but also in raising awareness of clinical research as a care option and dispelling common myths that may discourage participation.

Despite the influential role medical professionals have, only one-third of these respondents have ever talked about research with their doctor.

Patient communities and advocacy groups can help bridge the knowledge gap to improve health literacy, give patients access to former clinical trial participants, provide information about clinical trial opportunities, and direct patients to the best places where they already are searching for information—online.

To that end, we also need to be smarter about our methods of communicating. Digital solutions provide one avenue to reach patients, but we need to think about how we leverage digital tools to facilitate two-way conversations. While we understand that interpersonal communication with medical professionals is an essential part of the patient recruitment, screening, and consent process, too often we limit important conversations by failing to use all the tools available, like message boards and online communities.

These avenues are important: Our survey revealed that about three in five respondents use message boards and health-based online communities to learn more about their condition and the experiences of other patients. And about two-thirds of melanoma, gastrointestinal disease, lung cancer, lupus, and type 1 diabetes patients use message boards and health-based online communities to learn more about their condition and the experiences of other patients. This is particularly true among younger digital natives.

Yet, as any behavior change specialist can attest, information is not enough. As an industry, we must also remove barriers to participation by considering the burden placed on participants as the trials are designed. The industry needs to include better and more robust mechanisms for patients to participate at early stages of research planning from protocol design to endpoint selection.

This collaborative approach has been supported by the FDA as well. Under PDUFA V, the agency is conducting disease-specific patient-focused drug development (PFDD) meetings with key stakeholders to obtain patient perspectives on specific diseases and treat-
It is important to have mechanisms to quickly engage patients once they express interest in a clinical trial, and our data clearly show that the majority of patients would prefer that follow-up include interpersonal communication.

Conclusions
At the start of the survey project, we set out to answer the question: How can researchers engage patients in a way that makes them feel like stakeholders, rather than subjects, in research? What we learned is that while different patient populations have different specific desires, the underlying theme is that patients want more information from medical professionals, advocacy groups, and their peers.

The key takeaways from our efforts include:

1. Patients want to be well-informed and empowered consumers of health information.
   • Industry has a role to play here, especially with regard to health literacy. Reallocation of marketing spend from advertisements to educational materials or grants for health-focused nonprofit organizations may aid in developing the confidence healthcare consumers need to consider clinical trials as a care option.

2. We need a more collaborative planning process that incorporates all stakeholders, especially patients.
   • Patients want a say in what new treatments are researched and how they are tested, and they are willing to share their ideas and thoughts through participatory design processes. Having the right trial design for the right patient population may significantly reduce recruitment timelines and get new treatments to market faster.
   • There is a benefit to leveraging patient communities and advocacy groups since they are patient-focused and understand the nuances of specific conditions. Our research found what motivates patients to participate in a clinical study varies with condition and other demographic data, and patient organizations have valuable insight into engaging these patient groups. Patient advocacy groups are also expert communicators and can convey information about clinical trials and answer questions and concerns from patients and caregivers when they are seeking that information.

3. Data and technology companies and collaborations are increasingly important, but a human touch is still necessary.
   • The addition of electronic health records (EHRs) to identifying sites with potentially eligible patients can further add to the recruitment funnel, but without an understanding of which patients are interested in participating in medical research, these initiatives can fail flat.
   • It is important to have mechanisms to quickly engage patients once they express interest in a clinical trial, and our data clearly show that the majority of patients would prefer that follow-up include interpersonal communication.

4. Build lasting relationships with patients for improved retention, repeat study consideration, and continuous process improvement initiatives.
   • Treat patients as the research stakeholders they are and establish an ongoing flow of easy-to-understand information about the study progress and results to all participants during and after the trial.
   • Utilize surveys and focus groups. Data collected from patient surveys and/or focus groups can inform future protocol design and clinical endpoints selection and facilitate investigator quality management.
   • Create long-term relationships with patients before, during, and after the study with ongoing engagement programs that are specific to their preferences and needs.

As an industry, we need to do a better job of two-way communication from the start of trial design through to sharing the results. Patients are stakeholders in the research process with an equally strong interest in seeing new treatment options come to market. Yet, the barriers we present to their ability to engage with the research process in a meaningful way outside of clinical trial participation limit this collaboration and may reinforce feelings of unease and distrust. By improving our mechanisms for listening to and engaging patients at all stages of research design in a way that is meaningful to them, we can finally begin to move the needle on patient-centricity and truly understand the power the concept holds.

Lindsey Wahlstrom-Edwards, MPH, CPH, is Head of Partnerships, Antidote Technologies Inc.; Anne-Marie Hess is Senior Strategic Advisor and Director of Market Intelligence, SCORR Marketing
The Evolution of Patient Centricity

Moe Alsumidaie

Examining the distinct actions and advocacy that have advanced the concept from buzzword status to practical implementation in clinical studies.

Since we started reporting on the topic of patient centricity back in 2014, we’ve kept track of how the subject has evolved. Initially, there were many perspectives on what patient centricity was until the FDA started to evangelize its outlook on the matter. Nonetheless, the topic continues to present new opportunities with the emergence of digital health and is even propagating to smaller biopharmaceutical enterprises. In this article, we will discuss the start and evolution of patient centricity.

The start of patient centricity

While the FDA was working on the Patient-Focused Drug Development Initiative (since 2012), the first time we heard about patient centricity was during former FDA Commissioner Margaret Hamburg’s 2014 speech at New York BIO. During this speech, Dr. Hamburg elaborated on how the FDA had meetings with patients and patient advocates to discuss certain diseases, and how these diseases impacted patient lives. This effort allowed the FDA to understand diseases better, and how to develop more effective and user-friendly medical interventions. This initiative sparked a new wave that shaped the way the industry currently engages and involves patients in drug development.

Patient centricity: What you see is all there is

Despite the vagueness of patient centricity, the biopharmaceutical industry wasted no time and started discussing their perspectives about patient centricity at industry symposia. Most perspectives circled one theme: to involve patients in studies. The definition of “involvement,” however, differed between various industry leaders and service providers. To some, patient centricity meant providing patients better access to finding studies, or using technology and mHealth to make studies more convenient and “centric” to patients, whereas to others, patient centricity meant reducing patient burden by obtaining data from patient medical records. For example, GlaxoSmithKline executed the Salford Lung Study to evaluate chronic obstructive pulmonary disease (COPD) exacerbations with Breo Ellipta in real-world settings; rather than requiring patients to adhere to the confines of clinical trial constraints, GSK integrated into electronic medical record systems to collect endpoint-related data.

FDA steps in to define patient centricity

In 2016, the FDA evangelized how it perceived patient centricity and clarified industry misconceptions. According to our reporting with FDA, the industry wasn’t involving the patient during the entire drug development process, and that the industry should focus on why they are bringing drugs to market, incorporating patient diversity, and generating outcomes meaningful to patients. FDA suspected the disconnect in patient centricity interpretations arose from C-suite level personnel within the biopharmaceutical industry. Table 1 (see facing page) illustrates these differences.

Industry aligns messaging with FDA and focuses on industry-specific needs

In the following year, we started to see the emergence of perspectives that aligned more closely with FDA. For example, Novartis described patient centricity as “understanding the patient and the impact that we have and that we want to have on their lives…and where our therapeutic interventions can make a real difference.” Novartis pushed industry definitions by elaborating that patient centricity also involved reducing patient burden (i.e., eliminating unnecessary clinic visits or bringing the trial entirely to the patient’s home), while also reinforcing the desire to engage, inform, empower, and thank patients for participation, and focused on incorporating digital health initiatives in studies.

Similarly, Boehringer Ingelheim focused on investigating patient-centric efforts on remote trials, including leveraging digital opportunities (i.e., internet, social media, etc.) to recruit patients; using eConsent; collecting data remotely via biosensors; eMonitoring (i.e., leveraging risk-based monitoring on collected data); utilizing technology to engage patients (i.e., digital reminders, and digital access to study information); and pointed to a federal register docket on use of digital technology in clinical trials. In essence, BI was...
homing in on these initiatives to align its clinical trials with future patients, who will expect convenience and remoteness in study conduct. Service providers have also aligned with industry needs by tagging patient centricty with concierge services, such as Lyft rides to study visits.11

Patients reveal some evidence of industry alignment with FDA

While patients have suggested alignment with industry-led patient-centric initiatives by demanding convenience (i.e., remote study visits), incorporating digital health in study procedures, requiring sponsors to provide more information about study procedures, and designing protocols with the patient in mind, they have also indicated strong support that the industry is aligning with FDA patient-centric definitions by involving patients throughout the drug development process. For example, sponsors are offering genomic sequence data to patients through portals and hosting quarterly webinars to answer study-related questions. Shelly Hoover, an ALS patient, stated, “by bringing me in the process and sharing information with me, I feel like I am a more valuable contributor because I can see that what I am doing is making a difference and that the data is valuable to the people who are gathering it.”

Digital health influences patient centricty

With advances in digital health, Sponsors started to take the initiative by piloting studies that support the creation of tools for patient centricty. For example, Amgen launched a fully remote clinical trial using eConsent, Apple Watch, and electronic patient-reported outcomes (ePROs) to study a digital biomarker for migraine.12 Additionally, with FDA’s Digital Health Innovation Action Plan and the Pre-Cert program, service providers have emerged with a sole focus on advancing remote trials and are linking such services with patient centricty.

An evolving target, but gaining ground

In this article, we discussed the evolution of patient centricty over the past five years. The concept morphed from numerous theories into distinct, yet evolving approaches driven by the industry and regulators. It appears that the industry is starting to incorporate FDA’s perspectives of patient centricty in studies (i.e., patient involvement throughout the drug development process), and the industry is pushing its own initiatives that focus on bringing clinical trial convenience to patients via digital methods. We forecast that digital health will continue to influence patient centricty, as these technologies will allow studies to become more remote, hence, reducing patient burden. Additionally, we see that patient centricty will become a normal process in the biopharmaceutical industry, as smaller enterprises are starting to employ patient-centric approaches in drug development.

References

1. https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm

Moe Alsumidaie, MBA, MSF, is a thought leader and expert in the application of business analytics toward clinical trials, and Editorial Advisory Board member for and regular contributor to Applied Clinical Trials
Portfolio Approach to Optimize Site Selection

Vadim Paluy, MD, Vladimir Shnaydman, PhD

Optimization model evaluates the benefits of selecting a portfolio of investigative sites based on advanced analytical models.

Site selection is one of the most important and at the same time challenging problems in clinical trials planning. Poor site selection may cause enrollment delays, resource waste on low or zero enrollment, and even potentially compromise trial results.

Site selection is a complex process, which includes sites identification, sites assessment, sites validation, and selection of a set of sites aligned with study goals and limited resources.

Many factors affect the site selection process. Some of them are generic, others are trial-specific (Figure 1). Some factors are qualitative and subjective, such as “experience and qualifications of principal investigator (PI)” or “staff turnover.” The value of each factor can be evaluated qualitatively (e.g., excellent – 10, the worst – 1). Or it can be quantitative, such as “planned patients” enrollment” or “projected enrollment rate.” The factors could be extracted from historical databases, questionnaires, etc. Some companies use data-mining techniques for site identification. Examples of clinical trial-related factors are “trial budget,” “enrollment target,” etc. A variety of business rules are also related to the entire trial, e.g., “If a country is selected, then minimum two sites per country should be selected,” or “priority site”—forced site prioritization.

Traditionally, site selection efforts are focused on a selection of “best” clinical sites based on:

1. Predicted enrollment rates.
2. Predicted/planned site capacity.

3. Scoring of multiple site attributes (e.g., experience of PI and staff, historical patient enrollment rates, overall facility quality, etc.) and ranking index calculation as a sum of weighted scores.

4. Handpicked approach to sites selection based on prior relations with sites and sites’ qualitative evaluation.

Site rankings according to a criteria has limitations. For example, site selection based on sorting of predicted enrollment rates does not take into account parameters like cost per patient, site capacity, or “soft” attributes such as experience of PI, facility quality, etc. The value of site selection based on extrapolation of historical performance may be limited due to high site turnover or...
a limited or lack of historical data for new sites. Site selection based on sorting of ranking index also does not take into account budgeting and other constraints, as well as study goals and business rules.

Often, the site selection process mistakenly identifies with only site identification and feasibility assessment. After identifying the "best" sites and evaluating them, it is assumed that the best sites will be selected somehow from a feasible set of "best" sites.

Often, a feasible set of sites is identified based on an informal process which may include, but not be limited to:
1. Contact familiar sites.
2. Call on referrals.
3. Literature and database search.
4. Phone interviews and site visits.
5. Contract negotiations.

More advanced techniques (AI, data mining) could be applied for large sites’ databases but not transferrable to all sites.

Usually, all feasible sites are divided into three major tiers. Their advantages and disadvantages are presented in Table 1.

Sites could "migrate" from tier to tier depending on most recent performance assessments.

A high-level overview of the traditional site selection process is presented in Figure 2 and described below.

1. From sites database (A) (it could be proprietary or commercial), a feasible portfolio of sites is defined based on certain attributes (e.g. "A list of doctors treating multiple sclerosis in USA").

2. Then, all feasible sites are assessed based on scoring of each site attribute and its weight (B). A list of attributes may include: (1) experience of PI and site employees; (2) geographic location; (3) transportation to the site; (4) enrollment risk; and many others. Each attribute is scored (e.g., from 1 to 10) and weighted (in %). A list of attributes can be trial-specific. Scores and weights could be obtained from questionnaires, previous experience, historical data, etc. Small companies usually rely on questionnaires. Then, site value is calculated as follows:

\[
\text{Site Value} = \sum (\text{Param } (i) \times \text{weight } (i))
\]

After site evaluation, all feasible sites are ranked according to their value or other criteria.

3. As mentioned, ranked sites are divided into three tiers. First, sites from Tier 1 are selected, then from Tier 2, and if there are not enough patients or other goals have not been met, from Tier 3 — (C). Then, preselected portfolio of sites needs to be aligned manually with available budget, enrollment target, sites capacity, number of patients, and other goals and rules. If site selection meets study goals, site selection is finalized (F). If not, but other feasible sites are available (D), they need to be included in the selection process (E) with subsequent alignment to study goals and available resources (C), etc.

4. If number of feasible sites is not sufficient (D), a new search in sites’ databases needs to be performed (A).

5. It is assumed that after multiple iterations, site selection is finalized (F).

### Sites Classification

<table>
<thead>
<tr>
<th>Tier</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Most attractive, reliable sites, high enrollment</td>
<td>• Sponsors and CRO compete for Tier 1 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limited site capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Expensive</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Plausible sites, less expensive than Tier 1 sites</td>
<td>• Riskier than Tier 1 sites</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Problem sites. Cheapest sites. Used as backup sites</td>
<td>• Riskiest sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low enrollment</td>
</tr>
</tbody>
</table>

**Source:** Paluy et al.

**Table 1.** Tiered advantages and disadvantages of sites.

### High-Level Overview

- **Final site selection**
  - Sites valuation/reevaluation.
  - Ranking feasible set of sites based on their value, enrollment rate, patients availability, etc.

- **Select a feasible set of countries/sites**
  - From sites database

- **Adding/deleting ranked sites**

- **Preliminary site selection**
  - Manual alignment with study goals, budget, enrollment target, etc.

**Source:** Paluy et al.

**Figure 2.** Traditional site selection process.

Let’s consider an example illustrating the site selection approach based on sites’ rankings.

**Case study: Contingency planning for Phase III CNS global clinical trial**

For a Phase III trial, an initial set of sites was already selected. However, some sites canceled their participation due to various reasons. Therefore, in order to meet study goals (enrollment rate, number of patients, and limited budget), there was a need to select additional sites. Twenty-five new feasible sites were identified.

Site selection needed to meet the following goals:

- Number of patients should be ≥ 85
- Enrollment target ≥ 5pt/month
- Budget ≤ 1.26 million

The technique included several steps:

1. Sites evaluation. Multiple site attributes were identified, as presented in Table 2 (see page 30). Some of them may be unique for a trial.
2. Site value is calculated according to the formula [1].
3. Sites are ranked according to their value (or other attributes such as predicted enrollment rate could be used as well). Data used in the ranking and the ranking results are presented in Table 3 (see page 30).
Ranking algorithm for site selection

Sites parameters, such as number of randomized patients, projected enrollment rate, and patient-related costs, are accumulating until their values meet or exceed study goals. For example, cumulative number of patients, cumulative enrollment rate, and cumulative site costs are obtained by adding site #2 data to the site #6 data (Table 3). It means that cumulative number of patients = 10 (site #6) + 10 (site #2) = 20. The same applies to projected enrollment rate for sites #2 and #6 = 0.52 (site #6) + 0.24 (site #2) = 0.76, etc.

Unfortunately, often study goals cannot be met simultaneously. For example, sites-related budget was met by adding site #4, but enrollment target goal was not met. Therefore, according to the ranking algorithm, sites #10 and #11 have to be added to meet the enrollment target goal. It means that budget was exceeded by $147,500, or by 12%.

If sites are ranked according to their enrollment rate, budget has to be increased by 8%.

This process is time- and labor-consuming and does not guarantee optimal site selection. Adding more sites does not solve the problem, because it is associated with increased cost of a clinical trial beyond the budget and inclusion of riskier sites into a pool of feasible sites.

Is there a better site selection solution aligned with study goals and within the budget?

This paper presents a portfolio approach to site selection similar to selection of financial portfolios or portfolio of projects. For site selection, this approach was formulated in [1].

Portfolio approach to site selection

Portfolio approach to site selection means that instead of selecting individual sites, clinical trial planners need to select a portfolio of sites based on advanced analytical models, where the goal of site selection is to maximize the overall value of a portfolio of sites, and to align it with clinical trial goals and limited resources. As shown in [2], the most effective approach to portfolio selection is based on the mathematical optimization model. The model replaces the loop, including steps B (except sites evaluation), C, D, E, with advanced modeling algorithms, automating site selection aligned with study goals and resources.

<table>
<thead>
<tr>
<th>Sites Evaluation</th>
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<th>List of site attributes could be trial specific</th>
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<td>Country</td>
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<td>C2</td>
<td>C3</td>
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<td>Weight</td>
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<td>10</td>
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<tr>
<td>Experience and qualifications of study coordinator and other staff</td>
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<td>7</td>
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<tr>
<td>Availability of suitable patient population</td>
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<td>8</td>
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<tr>
<td>Accessibility of diagnostic or therapeutic equipment</td>
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<td>9</td>
<td>8</td>
<td>10</td>
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<tr>
<td>Track record with previous, similar trials</td>
<td>5</td>
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<td>5</td>
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<tr>
<td>Academic or “thought leader” credentials</td>
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<td>Geographic location (including international)</td>
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<td>10</td>
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<tr>
<td>Anticipated rate of patient accrual</td>
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<td>6</td>
<td>8</td>
<td>8</td>
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<td>Timing of Institutional Review Board meetings</td>
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<td>Contractual and budgetary negotiations</td>
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<td>7</td>
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<td>Regulatory history (FDA onsite, “blacklist”)</td>
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<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total value</td>
<td>7.76</td>
<td>7.98</td>
<td>7.76</td>
<td>6.19</td>
</tr>
</tbody>
</table>

Source: Paluy et al.

Table 2. Fragment of site value assessment.

<table>
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<th>Value Rankings</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tr>
<td>Sites</td>
<td>C1</td>
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<td>C3</td>
<td>C4</td>
<td>C5</td>
<td>C6</td>
<td>C7</td>
<td>C8</td>
<td>C9</td>
<td>C10</td>
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<tr>
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<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Value</td>
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<td>9.35</td>
<td>8.66</td>
<td>7.98</td>
<td>7.8</td>
<td>7.76</td>
<td>7.58</td>
<td>7.58</td>
<td>7.52</td>
</tr>
<tr>
<td>Total value</td>
<td>147.6</td>
<td>144.4</td>
<td>137.6</td>
<td>119.5</td>
<td>85.9</td>
<td>101.4</td>
<td>92.9</td>
<td>89.9</td>
<td>92.9</td>
<td>87.3</td>
</tr>
</tbody>
</table>

Source: Paluy et al.

Table 3. Sites are ranked according to their value.
Optimal site selection

In the context of decision-making, optimization means determining the most favorable solution, outcome, or course of action from a set of alternatives that satisfies all constraints and dependencies based on the mathematical optimization model.

In order to optimize site selection, an optimization model was developed. The model was formulated as a mixed integer programming (MIP) model. The MIP models are a subset of the linear programming (LP) [3] models, where some variables are binary (0, 1). LP models find the globally optimal value (e.g., total value of selected sites) of a linear function of a certain number of variables, given a set of linear constraints on these variables (equalities or inequalities).

The model for optimal site selection includes four components:

A. Decision variables

Xi = (0 or 1). Their value will be defined automatically. If Xi = 0, i-th site is not selected. If Xi = 1, i-th site is selected.

B. Parameters

Estimates for each site, such as cost/patient, projected enrollment rate, and others.

C. Constraints

1. Business rules (forced site prioritization, minimum number of sites per country if a country is selected), requirements for patients’ allocation across regions, and others.
2. Resources—budget, manpower, etc.
3. Study goals—number of patients to be enrolled (trial power), enrollment target, etc.
4. Other rules relevant for particular clinical trial.

D. Criteria

Single (e.g., maximum value of sites’ portfolios), or multiple criteria (maximum enrollment target, minimum budget, etc.) can be used.

Modeling experiments

The model (Site Selection Optimizer) uses the same data as presented in Tables 2 and 3. The optimization algorithm found a better solution than the one based on the ranking algorithm. It automatically selects a portfolio of sites aligned with study goals and budget (Table 4). At the same time, in order to reach study goals, ranking algorithm requires ~12% bigger budget and more sites (17 - ranking vs. 16 - optimization).

Selected portfolios of sites using ranking vs. optimization (baseline scenario) are presented in Table 5.

Optimization results may not look intuitive. For example, site #2, despite its high score/value, was not selected due to high costs/patient, high number of patients, and total costs/site. Also, site #2 was not selected because of a “knapsack effect.” That means that it’s harder “to pack” a large site (site capacity = 10 pt) vs. several small “items” (most sites capacity =5 pts). Sites #9 and #16 were selected in the optimization model despite their relatively low score, because cost/patient is low and enrollment is high enough.

The model validation table is presented in Table 6 (see page 32).

Could the solution presented in Table 6 be obtained without the model? Potentially, yes. However, more than two million portfolios have to be analyzed, and the probability of picking up an optimal portfolio of sites ~1/ (2*106) is similar to winning the lottery. Therefore, in a reasonable timeframe, only suboptimal portfolios could be generated. At the same time, for the case study, the model generated an optimal portfolio of sites in two seconds.

Model advantages:

1. Flexibility (ability to modify the model according to customer needs).
2. Uncovering best solutions.
3. Flexibility (ability to modify the model according to customer needs).
4. Other rules relevant for particular clinical trial.

### Table 4. Ranking vs. optimization in site selection—high-level results.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Target</th>
<th>Ranking</th>
<th>Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budget, M</td>
<td>1.26</td>
<td>1.41</td>
<td>1.26</td>
</tr>
<tr>
<td>Enrollment rate (pt/m)</td>
<td>5.0</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Trial power (#pts)</td>
<td>85</td>
<td>98</td>
<td>88</td>
</tr>
<tr>
<td>Number of sites</td>
<td>min</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 5. Selected sites, ranking vs. optimization.

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>Value</th>
<th>Ranking</th>
<th>Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C1</td>
<td>7.76</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>C1</td>
<td>7.76</td>
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</tr>
<tr>
<td>3</td>
<td>C1</td>
<td>7.48</td>
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<td>4</td>
<td>C1</td>
<td>7.48</td>
<td>1</td>
<td>1</td>
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<tr>
<td>5</td>
<td>C1</td>
<td>7.58</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>C1</td>
<td>7.58</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>C1</td>
<td>7.58</td>
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<td>1</td>
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<tr>
<td>8</td>
<td>C1</td>
<td>7.58</td>
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<td>1</td>
</tr>
<tr>
<td>9</td>
<td>C1</td>
<td>7.32</td>
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<tr>
<td>10</td>
<td>C2</td>
<td>7.42</td>
<td>1</td>
<td>0</td>
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<td>11</td>
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<td>7.42</td>
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<td>1</td>
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<tr>
<td>13</td>
<td>C2</td>
<td>7.37</td>
<td>0</td>
<td>1</td>
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<td>14</td>
<td>C2</td>
<td>7.37</td>
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<td>15</td>
<td>C2</td>
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<td>16</td>
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<td>17</td>
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<td>7.42</td>
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<td>18</td>
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<td>7.42</td>
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</tr>
</tbody>
</table>

Source: Paluy et al.

- High enrollment rate.
- Low cost/pt
- Minimum two sites/country

Source: Paluy et al.

- High cost/pt
- Low enroll.
3. Fast and comprehensive analysis of multiple “what-if” scenarios.

The model allows the calculation of multiple metrics related to multiple parameter allocations across countries, such as clinical trials costs, clinical sites, patients, and enrollment rates, as presented on Figure 4.

‘What–if’ scenarios: Exploring this model’s capabilities

Scenario #1. Forced selection of site #2 (see Table 7 on facing page).

In order to meet study goals, forced selection of site #2 (high value, but low enrollment rate (see Table 6) modifies baseline solution. For example, sites #6, #9, #14, and #25 were not selected. At the same time, sites #10, #19, #21 were selected. Also, this scenario requires higher budget ($1.34 million vs. $1.26 million in baseline scenario) and a larger number of sites (16 in baseline scenario vs. 17 in scenario #1).

Scenario #2. Forced removal of sites #6 and #15 (see Table 8 on facing page).

At the last minute, sites #6 and #15 decided not to participate in a clinical trial. The model recalculated the sites’ portfolios. In this case, the number of sites was increased by two (from 16 – baseline scenario), to 18 (scenario #2). Budget was increased from $1.26 million to $1.30 million.

Model enhancements

1. Multi-criteria model

Very often, it is hard to meet all requirements by using a single criteria optimization model. In some cases, multi-criteria optimization could be more effective in instances of multiple conflicting goals. The model modification requires the introduction of multiple criteria (in our case, “Maximum Value,” “Minimum Budget,” and “Maximum Enrollment”). Each criteria has a weight in %. Sum of weights = 100%.

Five scenarios were compared against the baseline optimal site selection scenario (see Table 9 on facing page). The first three scenarios (S1, S2, and S3) are equivalent to a single criteria optimization (weight of a criteria = 100%), scenario S4 is associated with highest weight=50% on criteria #2 - “Minimum Budget”, 30% weight on crite-
ria #1 - “Maximum Value”, and 20% weight on criteria #3 - “Maximum Enrollment.” Scenario S5 is associated with equal weight to all three criteria – 33.33%. The model generates different portfolios of sites for each scenario presented in Table 10 (see page 34). It was noticed that there are sites selected in all scenarios, e.g., sites #5, #7, #11, etc., and sites not selected in all scenarios, e.g., sites #17, #18, etc.

2. Stochastic enrollment

One of the challenging aspects in site selection is uncertainty in enrollment predictions. At the same time, deterministic site selection has to be made. In order to address this issue, the model was modified. Three enrollment scenarios (favorable, realistic, and conservative) and corresponding subjective probabilities for each site were considered instead of the deterministic enrollment rate in the baseline model (see Figure 5 on page 34).

The stochastic model may generate different solutions than the deterministic one. For example, site #5 in Table 11 (see page 34) was selected in the deterministic model, and not selected in the stochastic one. Inclusion of a site into a portfolio depends on other parameters involved in the optimization.

<table>
<thead>
<tr>
<th>site</th>
<th>Country</th>
<th>Value</th>
<th>Baseline</th>
<th>Forced selection site #2</th>
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Source: Paluy et al.

Table 7. Baseline scenario vs. “forced selection of site #2.”

‘What If’ Scenario 1

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Source: Paluy et al.

Table 8. Forced removal of sites #6 and #15.

‘What If’ Scenario 2

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Source: Paluy et al.

Table 9. Scenarios in the multi-criteria model for site selection.

Key points

- Site selection model generates optimal set of sites of highest value aligned with clinical trial budget, target enrollment, site capacity, site enrollment, clinical trial power and a variety of business rules.
- The model could significantly save time and money by automatically generating an optimal set of sites, minimizing decision-making delays, and enhancing the quality of decisions.
- The model was validated for a clinical trial. It produced better
site selection portfolios than the ranking model did, because
the required budget was 12% less in optimization than in rank-
ing. For multiple clinical trials, savings could be substantial.

- The tool could be integrated with any sites’ databases utilizing
both methodology of successful study start-up and specific tools
(e.g., enrollment forecasting, financial planning, benchmarking).

### Generated Portfolios

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**Source:** Paluy et al.

**Table 10.** Portfolio of sites for each scenario.

### Enrollment Scenarios

**Deterministic site selection**

P1, P2, P3 – subjective probabilities

\[
P1 + P2 + P3 = 1
\]

**Conservative enrollment rate**

**Moderate enrollment rate**

**Optimistic enrollment rate**

**Example:**

<table>
<thead>
<tr>
<th>Enrollment rate, pt/m</th>
<th>Conservative</th>
<th>Moderate</th>
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**Source:** Paluy et al.

**Figure 5.** Stochastic enrollment rate in site selection.

References


**Vadim Paluy, MD, is Clinical Research Medical Director, Novartis; Vladimir Shnaydman, PhD, is President, ORBee Consulting**
The Rise of Shared Digital Health Economy and Promise of Accelerated Clinical Research

Over the last decade, we have seen a massive “uberizing” transformation of consumer economy, in which individuals now have control of many of their personal properties to be made available to others at a price. As the shared economy continues to expand, we are seeing companies launching similar models around personal data.

This development could help address some of the biggest challenges in healthcare—delivering treatment and care for those with unmet needs, especially those people affected by rare diseases.

LunaDNA and Hu-manity.co are examples of companies looking to enable individuals to own and transact their medical data. Luna DNA received SEC approval of monetary values of an individual’s own genomic and related health data. While promising, it will take time to gauge major results, which begs the question—what’s being done now to develop therapies?

With treatments available only to around 5% of the 7,000 rare diseases, or about 10% of the 30 million affected individuals in the US, the challenge to take on rare disease is beyond just the numbers. Historically, the biopharmaceutical industry has gravitated away from rare disease drug development due to the perception of high risk and, ultimately, the profitability question. Nonetheless, organizations like the Cystic Fibrosis Foundation, which supported development of Kalydeco by Vertex, and other trailblazers in the non-profit patient advocacy space have begun to build a paradigm required to speed rare disease drug development due to the perception of high risk and, ultimately, the profitability question. Nonetheless, organizations like the Cystic Fibrosis Foundation, which supported development of Kalydeco by Vertex, and other trailblazers in the non-profit patient advocacy space have begun to build a paradigm required to speed rare disease drug development due to the perception of high risk and, ultimately, the profitability question.

The Children’s Tumor Foundation (CTF) has recently built a new integrated R&D accelerator model to provide critical resources and infrastructure, that has been lacking to researchers, to properly study and translate their studies into clinical programs. In this particular case, CTF focused on applying the model toward neurofibromatosis (NF). It established an NF patient registry to enable nature history studies and patient recruitment, an NF biobank to support researchers accessing well-characterized tissues and samples, a preclinical consortium, and an NF data hub. CTF also fostered a network of NF key opinion leaders, NF academic researchers, and NF clinicians for standardizing diagnosis and outcome measures.

Of all these elements, recruiting patients to participate is critical, and the 10,000-member NF registry has supported recruitment needs for 20-plus clinical trials. The establishment and availability of such infrastructure can affect the go/no-go decision for industry to invest in rare disease drug development.

We are seeing many other patient advocacy organizations swaying away from a traditional model of granting academic researchers to now supporting biotechnology and pharma companies. In addition to the financial grants received by Tocagen from the American Brain Tumor Association, National Brain Tumor Society, and Accelerate Brain Cancer Cure, the help from the patient advocacy organizations with clinical trial recruitment significantly reduced the recruitment barrier that many other companies almost always face, especially with rare diseases.

Another noteworthy patient advocacy organization is the Hereditary Neuropathy Foundation (HNF). HNF has been focusing on accelerating R&D for those affected by the rare disorder Charcot-Marie-Tooth (CMT) and other inherited neuropathies. Unlike other monogenic-based rare diseases, CMT is comprised of multiple genetic diseases, which makes it much more difficult and complex for researchers to study.

This amount of collaboration among industry, academia, government, non-profit foundations, and patient advocacy organizations has resulted from the unique sets of inherent challenges in rare disease drug discovery and development. And as other companies complement these efforts by continuing to build application programming interfaces (APIs) to enable individuals to share data easily within the research ecosystem, every rare disease patient will have the opportunity to help propel drug discovery.
We are constantly innovating.

Our goal is simple. Rapid access to, and analysis of, high quality data to speed up and improve decision-making to meet our customers’ needs.

ICON and You.
Partners making a difference.

ICONplc.com