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Your Peer-Reviewed Guide to Global Clinical Trials Management

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APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

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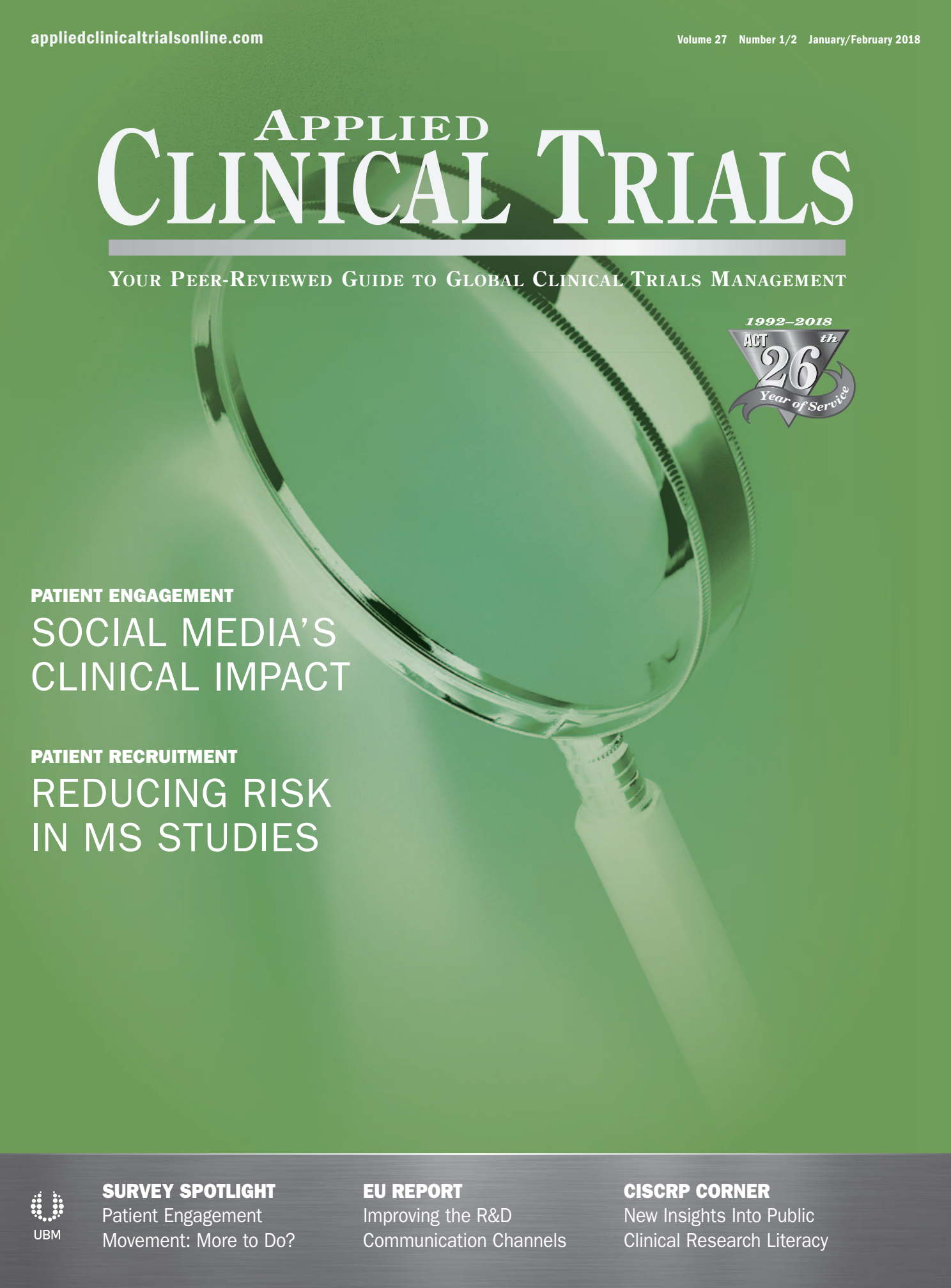

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Trials, Through the Eyes of Investors

LISA HENDERSON
Editor-in-Chief

Here is something that maybe you don't realize when you are knee-deep in managing a clinical trial, or trying your best to enroll patients, or implementing yet another software system that will "make your job easier." What you may not realize is that the success or failure of each trial represents a huge part of our economy. Be they stock market activity, investment funds, or venture capital, clinical trials and the "betting" on future successes is serious business.

Maybe I shouldn't be so naive. Maybe you knew that already. But I spent three days at the 36th Annual J.P. Morgan Global Healthcare Conference in San Francisco in early January; it was my first time going there, and it was definitely an experience. This is where the CEOs of life sciences companies of all sizes and flavors come to inform investors of their 2017 highlights, 2018 plans, their company financials, and hopefully come across as the next great place in which to invest.

I attended a number of sessions presented by small biotechs and for that I was immensely grateful for my knowledge of and experience reporting on the clinical trials industry. While a lot of the science was beyond me, it was still fascinating to hear the different approaches these companies are taking—mostly toward rare diseases, specifically in cancers. Many of the CEOs presented photos and backgrounds on specific patients, people showing great improvements in the trials, and putting a face and a name to the diseases they are battling.

During the event, on Jan. 8, Axovant announced negative results from a Phase IIB trial for Lewy body dementia. The company ended the program for its investigational compound and its stock dropped 50%. We talk about the costs of clinical trial failures many times, so we can assume the cost of its Phase II trial alone was slightly over $10 million. It was being conducted in 65 sites across the U.S., as well as Western Europe.

On brighter notes, ImmunoGen's CEO spoke to its candidate mirvetuximab soravtansine in Phase III trials for the treatment of platinum-resistant ovarian cancer. According to ClinicalTrials.gov, NCT02631876 aims to enroll 333 participants in its FORWARD I trial at 106 global sites. A Phase III trial of that size is approximately $20 million to conduct in oncology.

Meanwhile, other life sciences executives added their perspectives to the mix; among them was the recently renamed Syneos Health, representing the INC Research and inVentiv Health combination. According to CEO Alistair Macdonald, the merger brings the strengths of the number three CRO and number one CCO together to bring clinical insights into a sponsor's commercial strategy. Through positioning of its Integrated Solutions Group, the goal is to bring dedicated resources to the commercial dialogue earlier and continue the relationship well into the next stages of a drug's development. Macdonald noted that the CRO market is mature, and the CCO less so, and is banking on increasing revenue and penetration on that side of the business.

But as we see, involvement in the earlier stages of a drug may not always pan out. The balance of investment and science is a tricky art.

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PEER REVIEWED

12 How Social Media is Transforming Pharma and Healthcare

Nimita Limaye, PhD, Awani Saraogi

Outlining the growing attention and pursuits around social media in adverse event reporting and advancing patient-centric initiatives in clinical trials.

WASHINGTON REPORT

FDA STRIVES TO MAINTAIN GAINS IN SPEEDING MORE BREAKTHROUGHS TO PATIENTS

New drug approvals reached record levels last year, with FDA approving 46 new molecular entities (NMEs), more than double the number in 2016. Add to that the landmark gene and CAR-T cellular therapies and vaccines regulated as biologics. This achievement reflects a large number of applications filed with the agency for breakthrough cancer and rare diseases treatments that qualify for more streamlined clinical testing and accelerated review. Now the challenge to FDA and to sponsors is to maintain the high level of support for research, discovery, and regulatory flexibility underpinning these gains.

Whether approval numbers remain high in 2018 involves a range of factors. Several late 2017 decisions were scheduled for review this year, a process that often reduces review numbers in subsequent months: FDA approved 45 novel drugs in 2015, but only 22 in 2016. At the same time, the R&D pipeline is full: the Center for Drug Evaluation and Research (CDER) reported an increase in submissions last year and that it is overseeing more than 7,000 active investigational new drug applications (INDs) for drugs and biologics.

The ability of FDA and sponsors to expeditiously move important therapies through development and review reflects innovations in clinical research strategies and in regulatory policy. FDA is approving more critical treatments for life-threatening conditions based on results from small and early clinical studies. While some critics claim that such truncated clinical research puts patients at risk, FDA officials insist that it is maintaining high standards while paying more attention to risk-benefit assessments that reflect patient needs and preferences.

Maintaining momentum

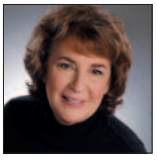
Further modernization of FDA medical product oversight remains a key goal for Commissioner Scott Gottlieb, who has rolled out multiple initiatives in recent months to better inform R&D policies. Many of these implement provisions of the 21st Century Cures Act that authorize more efficient clinical research strategies and more collaboration within FDA in reviewing innovative and challenging therapies. FDA launched the Oncology Center for Excellence last year, which was instrumental in approving new breakthrough gene therapies, and Gottlieb is considering additional cross-agency Centers to facilitate development of immunology and neuroscience treatments. Similarly, the Center for Biologics Evaluation and Research (CBER) established a framework for evaluating Regenerative Medicine Advanced Therapies (RMATs), issuing guidances and developing standards and definitions to help sponsors utilize the program.

FDA also is advancing programs to qualify drug development tools such as biomarkers, animal models, and clinical outcome assessments (COAs); a scale for assessing patient reported outcomes related to major depressive disorders is under review. And the development of new antibacterial medicines should gain from the Limited Population Pathway (LPAD) for testing treatments for infections in small patient populations. The Cures Act further encourages use of novel clinical trial designs, modeling and simulations for evidence of effectiveness, as well as for optimizing dosing and evaluating adverse events. And it supports broader incorporation of complex adaptive studies into clinical protocols, a topic that will be discussed at an FDA public meeting in March 2018.

New guidance published in December aims to further encourage development of targeted medicines that address underlying genetic mutations. The advisory supports enrollment of patients with rare mutations in clinical trials for promising therapies, including those that target a molecular subtype common across different phenotypes, such as Merck's Keytruda (pembrolizumab). A second guidance discusses the assessment and use of in vitro diagnostic (IVD) devices in clinical trials to determine if the IVD requires separate FDA review. The aim is to prevent clinical study failure due to uncertainties about biomarker validity. Further guidance will assess the risks related to certain IVDs used in oncology studies, with the goal of simplifying the development of companion diagnostics and their use in drug development.

FDA ended the year with additional advisories on how sponsors should best utilize a range of formal meetings and other means of communicating with agency staffers during drug development, with the goal of further improving the speed and efficiency of the drug approval process.

While it will be difficult for FDA to achieve another year of record approvals, the pace of policy development and regulatory innovation shows every sign of continuing at a fast pace. In recognition of the globalization of drug R&D, FDA aims to finalize new rules to facilitate the use of clinical data from outside the U.S. in evaluating medical devices and to update postmarketing safety reporting for drugs and biologics to fit international standards. With new research indicating that important gene therapies for sickle-cell disease and hemophilia are on the horizon, along with more cancer killers and rare disease cures, the pressure is on FDA and industry to smooth the path to further breakthroughs.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

1/18/18: Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance

1/3/18: Good ANDA Submission Practices Guidance for Industry (draft)

12/29/17: Establishing Effectiveness for Drugs Intended to Treat Male Hypogonadotropic Hypogonadism Attributed to Nonstructural Disorders (draft)

EU REPORT

COMMUNICATING R&D: PIPERS, PAYMENTS, AND PERSUASION

Everyone knows that research and development is where the costs must be met in creating new medicines. And everyone knows that keeping the money flowing in to fund the research is crucial. Just look at the thousands of investors and company executives at the recent JP Morgan Healthcare Conference in San Francisco for proof of how vital money is. Or look at Pfizer's new-year hesitations over keeping up its R&D into Alzheimer's and Parkinson's disease—that's a neat demonstration of what happens when money-men decide there is too much risk, and too little return.

But bioscience companies in the UK who want to play their own tunes do not know enough about persuading investors to fund the piper. That, at any rate, is the conclusion to be drawn from a "Best practice guide for communicating R&D progress to investors and the public" published in early January by the industry's energetic BioIndustry Association. The BIA describes it as a best practice guide for bioscience companies on how to maintain understanding and trust through their communications. It's all about how to ensure that people outside the research community fully appreciate the value of putting money into research, of paying the piper so he can make the best music.

"We need investors and the public to be well informed and confident about the great science our companies are doing," said BIA's CEO, Steve Bates, launching the guide. The need for clear and effective communication has never been greater, he argues. "Distilling complex ideas in high science companies for multiple audiences can be challenging," the guide says, introducing its advice for companies in planning their communications in an age of digital platforms and changing media.

And what does BIA see as the vital ingredients to affect this dramatic improvement in contacts between researchers and funders? Some of its recipe appears obvious to the point of dullness. Preparation of a regularly-updated communications plan focused on progress in a company's product portfolio, scenario-planning in advance of trial results (including "how positive, negative, and mixed results will be communicated"), and approaching target audiences directly, rather than just through regulatory announcements. Consistency in the timing of communications, or clarity and transparency, even with bad news.

All fairly standard and predictable advice; but the guide offers some counsel about relevance that is genuinely pertinent. "Be mindful of the impact on members of the public to whom it (i.e., the information) is personally relevant," it says. "Consider the effect the information may have on patients and their families, clinical trial participants, and others to whom it is personally relevant."

This amounts to a timely reminder to everyone engaged in the medicines sector—investors, researchers, company bosses, regulators—to bear in mind the ultimate objective of their endeavors. Yes, each player is motivated by his or her own personal goals, be they related to profit, prestige, or career advancement. But if the end-users are completely neglected in that rationale, suspicions of cynicism are likely to arise, particularly in a sector whose public pronouncements frequently invoke the concept of service to the community. And at that point, erosion can set in of the trust that is such a crucial factor in the relationship between the public and healthcare systems.

As a case in point, the possibility has been under discussion in the UK recently of somehow protecting pharma from the impact of Brexit, by leaving drug approval under European control even when the UK is no longer a member of the EU. Not a bad idea, perhaps, but the mood music about it has focused on how valuable this would be for the drug industry. The proponents appear to have overlooked the very obvious consideration that if exceptions should be made to Brexit to aid the drug industry, then exceptions to Brexit might equally well be entertained for the benefit of patients. Leaving them out of the picture suggests self-interest rather than enlightenment.

Regulators, too, are not immune to the risks of misperception of motive. Some spirited exchanges in the European Parliament in early January exposed a persistent gulf of misunderstanding between the European Medicines Agency (EMA) and many patient groups, as critics unleashed a volley of accusations that the agency allowed undue drug industry influence over its decisions. Responding to concerns that agency experts were not sufficiently independent, Noël Wathion, the deputy director of the EMA, demanded: "What do you want? A system with no experts?" He scored a debating point, but his approach to the discussion served to strengthen, rather than dispel, the suspicions among many critics that regulators are aloof, immune to suggestions that alternatives might be considered.

Whether it's innovators seeking sponsorship, industries seeking political support, or regulators seeking legitimacy, it's dangerous to forget that the essential bottom line of every communication is that simple appeal: "Trust me."

— Peter O'Donnell

EMA NOTES

ORPHAN DRUGS IN THE MARKET: The European Medicines Agency (EMA) will publish an orphan maintenance assessment report for every orphan-designated medicine which has been recommended for marketing authorization by the agency. View the first report here: bit.ly/2DC7Zzh

EMA IMPORTANCE TO EU CITIZENS: The EMA has published three animated videos to explain how the agency ensures that medicines are effective and safe for the benefit of patients across the European Economic Area (EEA). View the videos here: bit.ly/2E3dWmt

DATA MANAGEMENT

MAKING REAL-WORLD EVIDENCE REAL

Clinical trials tell us about the safety and effectiveness of drug and treatment therapies in carefully defined environments with carefully selected participants. But how will they perform in the full spectrum of medical use in an imperfect world? To answer that question, we're seeing a lot of interest in real-world data from various sources that represent much larger populations, broader eligibility criteria, and data from external sources such as health insurance claims data and electronic medical records.

Real-world evidence helps identify which patients will benefit the most, based on biological, social, and lifestyle attributes that might not be captured in clinical trials. Real-world evidence provides a clearer picture of a product's safety, effectiveness, economics, and value in day-to-day use. And it offers a deeper understanding of epidemiology trends and disease management, resulting in better diagnostics and treatment path.

However, real-world data can be massive, messy, and diverse; and most life science organizations aren't fully prepared to deal with it. Analytics systems are generally a patchwork of products and tools that don't speak to each other. It's hard to find data scientists who understand the intricacies and caveats of the data sources. Data queries are difficult and complex to write and take a long time to run, and this is often compounded by different groups unknowingly duplicating each other's work.

As researchers look for more predictive insight from huge streams of data, the traditional ways are no longer sufficient. It's time for life sciences organizations to formalize the platform and processes they use to create, govern, share, and reuse real-world data to drive critical insights.

RWE IN ACTION

Potential uses for real-world evidence approaches include:

- **Improving patient safety:** Identify subpopulations demonstrating unique risks to better inform risk profiles for products, procedures and services.
- **Obtaining real-world product insights:** Understand clinical effectiveness (as opposed to efficacy during a clinical trial), adherence, comparative effectiveness, product persistence and overall patient outcomes over time.
- **Improving marketing:** Better understand patient outcomes to improve brand planning and position new medicines in the therapeutic area.
- **Exploring valuation:** Use preference and performance data to quantify product/service market value and improve price negotiations.
- **Improving compliance:** Coordinate utilization, preference and consumer data to assess compliance and, when necessary, implement effective intervention programs.

The essential foundation

To formalize the management of real-world data and generation of real-world evidence, organizations must have six foundational capabilities:

1. A unified data architecture simplifies IT's role and ensures that all functional groups, such as epidemiology, commercial, and R&D groups, are working off the same page.
2. Moving data from a dedicated processing appliance ($20,000 to $30,000 per terabyte) to high-performance distributed computing (Hadoop, about $4,000/terabyte) saves $800,000 for every 50 terabytes of data.
3. While there will likely never be one common data model, tools can simplify and automate the processes needed to transform and standardize data, regardless of the source and target systems.
4. Well-governed data management ensures that data transformations occur the same way each time, only the right people are accessing the data, and data processes are maintained in a structured way.
5. Reuse of cohort definitions is supported once all data sources are mapped to a common data model, and you are defining cohorts in a consistent and repeatable way.
6. Templates for analytic use cases, such as signal detection, can be created and shared, which helps accelerate adoption, while more sophisticated use cases can be built on top of them. There's no need to reinvent the wheel.

Taking real-world evidence to the next level

Standardization and reuse of data transformations and analytics combined with advanced ad hoc analytics capabilities make real-world evidence faster and more consistent, repeatable, intuitive, and powerful.

Standard, customizable cohort builder

If you use a cohort builder, your choices have traditionally been a) easy-to-use tools that didn't do much, or b) sophisticated tools that required serious technical expertise.

The key for cohort builders today is to strike a balance between the two. Having an intuitive visual interface can support those who understand the population but don't necessarily know how to code, and can guide them through the process of specifying the criteria of interest. Such tools also support the complex query logic often required for these types of projects, such as multiple events and temporal relationships between activities or events in a patient's history.

Traditional and visual analysis

A visual analytics interface empowers non-technical users to do their own ad hoc exploration and streamlines the work of technical users. As a statistician, I can apply models, perform regression analysis and so forth in a visual tool that's working in memory. So now, I can fit models to my large data very rapidly, and I can hone in on which variables are important or of most interest. Then I can take that insight and do a more detailed, maybe hand-coded type of analysis of the data.

Advanced analytics for deeper insights

Advanced analytics changes the story from hindsight to insight and then foresight—

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Sponsors of biosimilar products made significant gains in 2017, though Research & Development and commercial challenges remain. Noteworthy news items included more and novel biosimilar approvals in ICH countries, including the first oncology biosimilar approval. There were also significant U.S. court decisions, such as the elimination of the patent dance, evolving and new innovator protection strategies, and promulgation of additional draft regulatory guidance, including those related to interchangeability and biostatistics.

This webinar will provide attendees an extended period of time to engage biosimilar experts from IQVIA's Biosimilars Center of Excellence (BCOE) to identify the key issues of 2017 – in a "Year in Review" format.

Attendees will hear three key case studies in order to discuss strategies to improve cost-effectiveness and patient access to originator biologics. The three case studies will examine:

- How biosimilar sponsors can extend their global development and marketing aspirations outside the EU and US markets
- How to expedite biosimilar clinical trial recruitment using secondary sources of data
- How sophisticated modeling tools can optimize your biosimilar protocol design

The webinar will then engage the audience to solicit insights from the BCOE experts in a "Meet the Panel" type format.

Contact IQVIA at www.iqvia.com

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

DATA MANAGEMENT

which is where organizations really need to be.

Unlike hypothesis-driven research, machine learning uses automated model building to adapt to what's happening in a population and finds things a human might not have thought to search for. With every iteration, the algorithms get smarter and deliver more accurate results. These methods have the potential to identify groups of patients who will benefit the most—or potentially be harmed by—a therapy.

Add value to your existing data investments

These foundation capabilities and enhancements translate into real value for life sciences organizations, especially considering the investments already made in the data sources themselves.

Managing real-world evidence in a well-structured, easy to use, and repeatable way is not just about wrapping up more projects in less time at less cost. It's about gaining insights to make decisions that deliver real value for your company and the patients who rely on your discoveries.

— Robert Collins is Senior Life Sciences Industry Consultant with SAS

NEWS NOTES

PARKINSON'S DISEASE CLINICAL STUDY REACHES MILESTONE

The Parkinson's Foundation announced the enrollment of the 10,000th Parkinson's patient and the discovery of critical new learnings in what represents the largest clinical study of Parkinson's disease in history. Launched in 2009, the study has grown from a small pilot to 29 expert clinics in five countries and serves as a platform for clinical studies to improve the lives of everyone with Parkinson's.

Specifically, the "Parkinson's Outcomes Project" evaluates the complete range of factors associated with Parkinson's disease: medications and other treatments, motor symptoms, cognition, anxiety and depression, and caregiver burden. The study, which includes more than 100 people who have lived with Parkinson's for more than 30 years and 83 people diagnosed before they were 30 years of age, covers more than 25,000 clinical visits and input from almost 9,000 family care partners.

Pfizer creates partnering model

Pfizer announced the creation of the Innovative Target Exploration Network (ITEN), a new, early-stage partnering model that enables collaborative relationships with select academic institutions and principal investigators around the world, to identify research projects that have the potential to deliver novel therapeutic targets and mechanisms of action to underpin future drug discovery in core areas of interest to Pfizer.

Roche acquires Ignyta

Roche and Ignyta, Inc. have entered into a merger agreement for Roche to fully acquire Ignyta at a price of $27.00 per share in an all-cash transaction. This corresponds to a total transaction value of $1.7 billion on a fully diluted basis. The merger agreement has been unanimously approved by the boards of Ignyta and Roche. Ignyta focuses on precision medicine in oncology aiming to test, identify, and treat patients with cancers harboring specific rare mutations. Its lead molecule is an orally bioavailable, CNS-active tyrosine kinase inhibitor being developed for tumors that harbor ROS1 or NTRK fusions.

Novo Nordisk establishes institute

The Novo Nordisk Foundation announced it will establish the BioInnovation Institute (BII), a center to develop and mature the best research projects in the life sciences in Denmark, with an initial investment of DKK 392 million (€51 million).

Celgene buys Impact Biomedicines

Celgene Corporation will acquire Impact Biomedicines, which is developing a kinase inhibotor for the blood cancers myelofibrosis and polycythemia vera. Under the terms of the agreement, Celgene will pay approximately $1.1 billion upfront and up to $1.25 billion in contingent payments based on regulatory approval milestones for myelofibrosis.

Charles River acquires KWS BioTest

Charles River Laboratories International, Inc. has acquired KWS BioTest, a contract research organization (CRO) specializing in *in vitro* and *in vivo* discovery testing services for immuno-oncology and inflammatory and infectious diseases.

Optimapharm lands MKS Research

Optimapharm, a CRO in South-Eastern Europe, acquired the Czech CRO MKS Research. By consolidating MKS Research, Optimapharm will have a total of 120 full-time employees and annual revenues over €12 million.

Pfizer halts Alzheimer's research

Pfizer has ended its search for new Alzheimer's and Parkinson's disease treatments. The company estimates 300 positions in the neuroscience discovery and early development programs will be eliminated. This decision follows years of costly failed drug trials. Pfizer will reallocate spending across its portfolio, focusing on its strongest areas. The company said restructuring will not affect research into drugs for rare neurological diseases.

Sanofi buys Ablynx

Sanofi and Ablynx, a biopharma company, entered into a definitive agreement under which Sanofi will offer to acquire all of the outstanding ordinary shares, including shares represented by American Depositary Shares (ADSs), warrants, and convertible bonds of Ablynx at a price per Ablynx share of €45 in cash, which represents an aggregate equity value of approximately €3.9 billion.

— Staff and wire reports

CISCRP CORNER

NEW INSIGHTS INTO PUBLIC AND PATIENT CLINICAL RESEARCH LITERACY

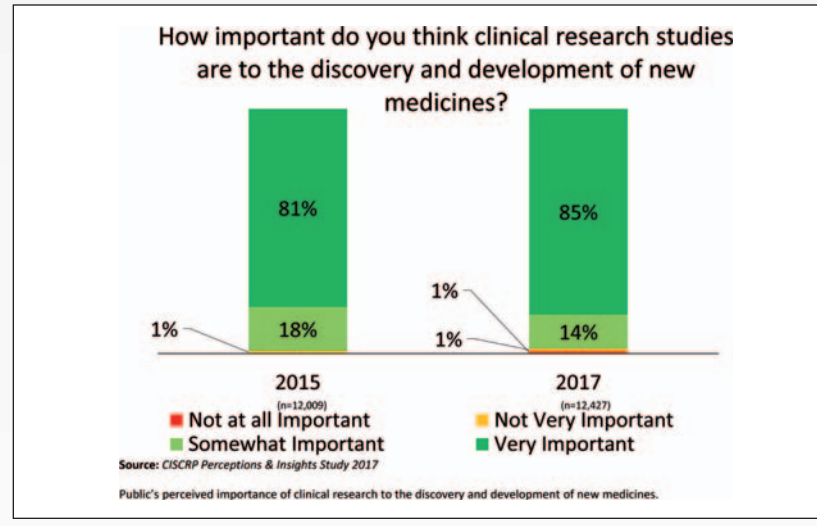
This article is the first in a series on the results of the Center for Information and Study on Clinical Research Participation's (CISCRP) 2017 Perceptions & Insights Study. Nearly 12,500 people worldwide responded—including the public, patients, and study volunteers—and provided valuable insights into opportunities to improve global education, outreach, and engagement.

Awareness and education gaps

The overwhelming majority of the public recognizes the important conceptual role that clinical research plays in the discovery and development of new medicines (see chart). This result holds even for those who have never participated in a clinical trial. North Americans and Europeans self-report being the most informed, with more than eight-out-of-ten indicating that they feel "Very" or "Somewhat Informed." People in the Asia-Pacific region report feeling the least informed (67%). Differences were also observed by age: The youngest age groups, made up of 18-34-year-olds, were more apt to report feeling less informed.

The vast majority (82%) of respondents overall believe that they understand the meaning of the term "clinical research study." A much higher percentage of women believe that they understand the term than do men. Approximately one-in-ten North Americans report that they do not understand the term well. This compares with 24% of respondents from Africa and 33% of respondents from Asia-Pacific reporting that they do not understand the term well. Age-related differences were also observed as a significantly higher percentage (20%) of 18–34-year-olds report that they don't understand the term at all.

But the results of the 2017 Perceptions & Insights study also reveal that the global public has a very superficial understanding about clinical research, suggesting education and outreach as areas of focus. Although a high proportion of the public say that they understand the term "Clinical Research Study," of those who self-report being "well-informed," two-thirds are unable to name an agency or organization that oversees clinical research safety and quality, and half (51%) say that they do not know where clinical research is conducted. Differences are observed by geographic region and age. In North America, Europe, and Asia-Pacific, 51%, 52%, and 54% of the public, respectively, say that they don't know where clinical research is conducted. Older respondents are more apt to know where research was conducted compared to younger age groups.



Public's perceived importance of clinical research to the discovery and development of new medicines.

Public confusion about the length of time that it takes to develop a new therapy and the proportion of drugs requiring clinical testing was also apparent. Four-out-of-ten people surveyed, for example, believe that it would take five years or less to develop a new drug or therapy.

Public trust and the perceived safety of clinical research is another critical aspect of overall clinical research literacy. A very high percentage believes that clinical trials are "Somewhat Safe" and "Very Safe," at 69% and 21% of total respondents, respectively. In this study, only 8% of North and South Americans believe that clinical studies are "Not Very Safe" and "Not at All Safe." This compares with 12% of the European public and 16% of the Asia-Pacific public sharing this view. Perceptions of clinical research study safety are also a function of age with a significantly higher percentage (14%) of 18–34-year-olds perceiving that studies are unsafe ("Not Very Safe" and "Not at All Safe").

The so what

These findings highlight opportunities—target audiences and educational content—for stakeholders to strengthen clinical research literacy, familiarity, and relevance and draw the public into a closer relationship with the clinical research enterprise.

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

Study methodology

The objectives of this study are to establish routine global assessments of public and patient perceptions, motivations, and experiences with clinical research participation in order to monitor trends and identify opportunities to better inform and engage the public and patients as stakeholders and partners in the clinical research enterprise.

Between May and July 2017, CISCRP conducted an online international survey. The survey instrument was based in part on questions posed in past surveys. CISCRP received input and support from pharmaceutical, biotechnology, and contract research organizations (CROs), and from investigative sites. A total of 12,427 respondents completed the survey. The online questionnaire was reviewed by an ethical review committee. CISCRP collaborated with Acurian, Clariness, CureClick, HealthUnlocked, and Quintiles to reach and engage respondents.

For more information about CISCRP's 2017 Perceptions & Insights study and to download reports, visit www.ciscrp.org.

Patient Engagement: More to Do?

Survey reveals a gap in the shift to true patient engagement, but overall measures show "centric" growth

PATIENT ENGAGEMENT

The latest survey results conducted with our partner SCORR Marketing show some rifts in the move toward more patient engagement in clinical trials.

With most of the respondents coming from academia or at the investigative site, another third were from the sponsors. More than half of the respondents said that there was no individual or department primarily tasked with patient engagement, and another 40% indicated they do not solicit input directly from patients for any of their patient engagement activities. This is somewhat surprising given the number of articles that *Applied Clinical Trials* has featured on the topic of patient centricity. A cursory search of our website brings up topics related to patient-centric activities to improve the trial experience, digital health tools to ensure patient engagement, outreach to advocacy groups to involve patients in the development of protocol design, and much more.

However, the survey did indicate that the two most important factors in the study design stage was to have a better trial design for patients, as well as identifying what were acceptable benefits and risks for patients.

At the clinical trial stage, patient adherence to medication dosing and site visits schedule was the primary reason for patient engagement activities, with higher patient retention and more satisfied patients tied for second. And after the trial, the longer-term goals for engaging the patient were to determine which outcomes were most important to patients, as well as encourage their future participation in clinical trials.

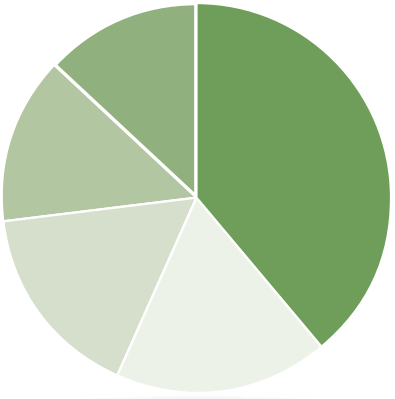
mHealth and technology

As mentioned, many reports show that mHealth and digital technology are increasingly being piloted or used in clinical trials as a patient engagement tool. However, our survey showed that most respondents believe in-person interactions were the most effective way to engage patients. Meanwhile, apps, web portals, social media, and chat or instant messaging all garnered around a five-out-of-10 for effectiveness.

Couple that with the question, "Has the use of technological innovations such as mHealth, wearables and companion apps provided a positive ROI?" with the following results: Unsure, 43%; No, 21%; and Yes, 21%.

Technology use could be a budgetary factor based on the results of the survey, which indicated insufficient study budgets were the biggest challenge to adopting patient engagement activities, as well as the most important factor of future implementation of patient engagement initiatives.

WHERE DO YOU GO FOR INPUT?



We don't solicit input from patients	39.5%
Surveys	18%
Other	16.5%
Patient communities	14%
Patient advocacy groups	13%

Source: *Applied Clinical Trials*/SCORR Marketing Patient Engagement Survey, December 2017

The response breakdown to survey question: "How does your company primarily solicit patient input so it can better design patient engagement initiatives?" Note: "Other" included doctors and databases.

Additionally, the survey showed an inexact science to measuring the effectiveness of patient engagement activities, or consistent metrics for evaluation. Most said that retention is their primary measure for engagement, followed by adherence. Almost a quarter do not measure engagement levels.

Overall, respondents do believe that patient engagement activities will increase over the next few years. Considering that patient centricity and patient engagement weren't given much attention until five or six years ago, we can take these results as a whole that clinical operations managers, directors, and staff believe that the patient centricity movement is intact and engagement activities are the necessary path to take. Please download the full survey report at http://bit.ly/2nCwthL.

— Lisa Henderson

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How Social Media is Transforming Pharma and Healthcare

Nimita Limaye, PhD, Awani Saraogi

Outlining the growing attention and pursuits around social media in adverse event reporting and advancing patient-centric initiatives in clinical trials.

PEER REVIEW

Social media has moved beyond being a fashionable word to one that is drawing renewed attention from the pharma and healthcare industries. The power of these tools and the impact that they can have not only on brand perception and, effectively, on sales, as well as the increasing interest of the regulators in social media is resulting in this shift. In addition, tools and technology and the growth of the data sciences industry have proven to be powerful enablers. As patient centricity becomes the cynosure of attention, the need to capture their views becomes necessary. Social media brings in a pragmatic component to clinical trials, supporting the world of evidence-based medicine (EBM). Patients themselves want to draw more informed decisions and want to be participants in the decision-making process on how their health is going to be managed.

It has been observed in studies that of the more than 74% of Internet users that engage on social media, 80% are looking for health information,[1] with 90% of the younger media-savvy 18-to-24 year-olds[2] claiming that they relied upon this source, using it twice as often as the more senior population. They shared health-related conversations and patient stories on diverse topics such as how someone coped with a chronic condition, views on diet and exercise, and their choice of physician.[2] The most accessed online resources for health-related information included WebMD (56%) and Wikipedia (31%).[3] Patients wanted doctors to actively share updates on the disease, new pipeline compounds, their experience with different drugs, etc., on social media and 60% claimed that they trusted what the doctors were posting.[4] It becomes all the more important for healthcare professionals (HCPs) to share accurate information and timely updates with the patient community. It was not only patients who were leveraging social media, 60% of HCPs were also actively watching what their counterparts are sharing on health-related issues. Doctors themselves seemed to truly believe that social media is impacting the quality of care. Forty percent of patients also relied upon social media to assess how others were dealing with chronic conditions.[2]

All of these situations have led to the development of numerous online patient communities such as:

- **PatientsLikeMe —** The largest online patient community, spanning 500,000 members[5] and covering over 2,500 conditions. It partnered with the National Quality Foundation to leverage social media to assess the quality of life in communities with multiple sclerosis (51,000 members), chronic obstructive pulmonary disease (2,500 members), and rheumatoid arthritis (10,000 members). They also compared patient-reported outcome (PRO) data generated from specific tools provided to these communities. Analyses showed that the PROs needed to use more "patient-friendly" language to describe the symptoms and it was the first time that such a large-scale study had been performed for an assessment of this nature.[6]
- **23andMe —** An online patient community to which the FDA granted authorization to market a direct-to-consumer genetic test, the Bloom syndrome carrier test; customers who purchase their personal genome service (PGS) would receive their ancestry information and uninterpreted raw genetic data.[7,8]
- **Iodine —** A site which combines pharmacist expertise, FDA data, and real-life experience from patients.
- **Smart Patients —** A closed online community which provides a platform for patients and caregivers to con-

nect amongst themselves and find disease-related guidance and answers that may be scant in other formal channels.

- **PatientsKnowBest —** A British social enterprise which integrates with the National Health Service (NHS) network and allows patients control of their own medical records.[9]
- **Doctor online networking communities —** Include those such as Doximity (has 70% of US doctors as verified members);[10] Sermo (with over 800,000 members across 96 specialties);[11] MomMD (women doctor's networking site, 11,000+ active members);[12] and many more.

Geo-based social media strategy

There is a whole spectrum of social media services being leveraged by pharma and healthcare, ranging across listening and analytics, marketing, and engagement. Companies are designing geography-based social media strategies based on the audience that they are targeting. Novartis, for example, thus engages with the public for its brand Gilenya® (the once-a-day pill developed to treat multiple sclerosis) through a dedicated handle on Twitter, @GILENYAGoUSOnly. The introduction section of this Twitter handle clearly calls out that it is only for a US audience and also sets forth other guidelines of interaction, such as the response window, how to share personal details, and also the discretion Novartis would practice in responding or not responding to certain tweets.[13] Internally, for a pharma company, this means the need for increased harmonization in social media efforts across countries and regions, while staying compliant with local regulations. When it comes to listening, social media tends to be more porous and it no longer matters, for instance, where an adverse event (AE) was reported, as it can find interested audiences anywhere in the world. But engagement is a different world altogether, as it has to be contextualized to the specific user, geography, local regulations, and so on.

More AE traffic?

The likelihood of generating excess AE traffic has been one of the reasons that often dissuades the pharma industry from leveraging social media listening. The four basic elements for submission of an individual case safety report to the FDA include an identifiable patient, an identifiable reporter, a suspect drug or biological product, and an adverse experience or fatal outcome suspected to be due to the suspect drug or biological product. Pharma companies are required to publish events reported on company-sponsored websites. However, if they do become aware of an event that has been reported on another site, they should review it and determine if it requires to be reported on their's. In recently reported industry views on the issue, Abbott felt that the entire web should be monitored for AE reports, while AstraZeneca did not align with this approach. Bayer allowed the Pharmaceutical Research and Manufacturers of America (PhRMA) to speak for the company, the group's stand being that only company-sponsored websites should be monitored and the events meeting the reporting criteria defined by the FDA should be posted, provided the reporters were privately contactable, so as to respect patient privacy issues. Lilly also observed that national privacy laws needed to be respected and follow-up with patients on these reports should be avoided. Merck & Co. cautioned that social media reports could result in an AE being blown out of proportion, citing the example of Sanofi, which had to shut down its Facebook page when a patient who reacted to cancer drug Taxotere posted a flood of comments about experiencing hair loss, triggering major reactions from the larger patient community. Sanofi did reopen the page later, but included terms of use. Lilly recommended that the FDA create a separate category for events reported on social media and also conducted a pilot study to demonstrate that the considerable efforts invested in monitoring social media for AEs did not yield corresponding results.[14]

The most significant challenge faced by pharma was identifying the reporter of AE information on social media sites. The FDA defines an "identifiable reporter" as one who is privately contactable. While Novartis believed that additional demographics were important, AstraZeneca felt that an email ID or even a Facebook contact was enough. However, both companies agreed that AEs collected from organized data collections systems should be considered as "solicited," whereas the rest should be treated as "spontaneous" reports. Though the European Union (EU) does not mandate the monitoring of social media for AEs, it does require that events that have been observed should be reported. This may change as observations from the WEB-RADR (Recognizing Adverse Drug Reactions) project gain traction in the EU. Launched in September 2014 by the Innovative Medicines Initiative, WEB-RADR, a €2.3 million, three-year public-private project, is responsible for developing a mobile application for reporting adverse drug reactions (ADRs) to regulatory bodies in the EU region. The mobile app would help evaluate the potential of social media data in identifying safety issues.[15]

It has also been observed that in a study conducted on AE reported for Lipitor® (atorvastatin) and Meridia® (sibutramine) in the FDA Adverse Event Reporting System (FAERS) database and on AskaPatient.com (a patient-support group website), the majority of AE reports on social media came from a younger population and focused on milder AEs on AskaPatient.com, as compared to those reported in FAERS.[16]

An evolving landscape

Pharma companies need to be mindful of varying regulations on the advertising of branded prescription products, while defining their product promotion strategy. It is very important, therefore, that each company develops its own social media policy guidelines. It has been observed that 23% of pharma organizations do not have policies to address data security and privacy, whereas 31% of healthcare organizations do have healthcare policies in place.[2] A review of the top 100 companies listed on the London Stock Exchange demonstrated that the top three social media-savvy pharma companies are Johnson & Johnson, GlaxoSmithKline, and Pfizer, respectively This becomes especially relevant when a company is marketing its products in multiple geographies, with varying local regulations. While this is acceptable in the U.S., advertising of branded prescription products is not accepted by many other countries.

In addition, when tweeting, one needs to be mindful of the FDA draft guidance on *Internet/Social Media Platforms with Character Space Limitations - Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices,* issued in June 2014.[18] This guid-

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ance specifically focuses on FDA-regulated medical products, the 140 character space limit associated with tweets, and the need of the pharma industry to present both benefit and risk information during product promotion while tweeting. While this does not apply to company websites, or product pages on social media websites such as Facebook or Twitter, the important take-home from this guidance is that irrespective of the character limitation, if a company is promoting the benefits of its product in a tweet, it also needs to bring to the attention of the consumer, albeit in a concise manner, the potential risks of the drugs as well, or else evaluate other platforms for product promotion.

Twitter, for its part, has been simplifying its rules, which gives pharma marketers some leeway. The site's 140-character limit has revised to 280, making it easier for benefits and risks to be included together. In a survey conducted by Ogilvy Healthworld with 14 big pharma companies, a 530% increase in the number of tweets in 2014 as compared to 2013 was observed. With access significantly enhanced, the need for regulations in this regard is understandable. Interestingly, the highest increase (300%) was noted in the activity of a key German drugmaker.[19]

One recent example of the FDA coming down hard on pharma social media practice was with respect to the promotion of Diclegis®, a Duchesnay's morning sickness drug, via social media posts from Kim Kardashian. The agency pointed out that while the posts highlighted the benefits of Diclegis®, the risks were not highlighted. This resulted in a warning letter being issued by the FDA's Office of Prescription Drug Promotion (OPDP).[20] It was one of 19 letters issued by the FDA, including three warning letters and 16 untitled letters.

Mining the web: who owns the data?

Not only do regulations regarding the posting of promotional information deter the pharma industry, but a large sector still perceives "listening" to be a liability. The key concern is that if companies do go down the social media path, they would need to notify regulators regarding all AEs identified by them on social media sites. The reality is that up to 90% of AEs go unreported and reporting by patients and HCPs is extremely low.[21] In efforts to address these gaps, Novartis and other pharma companies have been working on Web-RADR. Over three million posts from Facebook and Twitter (55% excluded as spam) were analyzed. Two percent were termed as "proto-AEs"—information which could represent potential AEs and were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Epidemico is developing algorithms to help detect potential AEs reported online and also eliminate duplicate reports. It is important to use a sophisticated, natural language processing system to eliminate the noise and draw meaningful results. About 12 drugs are being monitored by WebRADR and the data will then be analyzed by the European Medicines Agency (EMA) and the companies in the WebRADR consortium.

The ownership of such data—whether it should be the patient, the company, or regulator—is still being debated.[15,22] Patient advocacy group, EURODIS, which is associated with Web-RADR and represents patients with rare diseases, recommends that all data from social media be added to EudraVigilance, the EU's pharmacovigilance ADR database. This database is freely accessible to patients and researchers to aid signal detection. Currently, in the EU, companies are not obliged to scan social media and report AEs. However, if they do scan and find them, then they are obliged to report them to regulators. Regardless, it is mandatory for companies to monitor and report any side effects of drugs reported on their own sponsored websites.[23]

Drugmakers may have to reconsider their strategies for tracking AEs spontaneously, as the General Data Protection Regulation (GDPR) is set to go into effect in May. As per GDPR, the collection of any personally identifiable information (PII) by pharma would be regulated, provided the companies declare on their websites and social media properties that they are doing social listening and that the information shared by users may be used for this purpose. It is important to note that ethics-committee requirements vary from country to country and it is crucial that they also be examined so as to ensure compliance.

A good example of an ADR being identified through social media channels was the identification of "Crix belly" syndrome, also known as lipodystrophy syndrome, which results while taking antiretrovirals to treat HIV. It was detected using social media but was not identified during clinical trials, as the study duration was 48 weeks and the side effect manifested after that.[15] Patients themselves are screening multiple social media websites to find out more information about ADRs, and are sharing their experiences on sites such as PatientsLikeMe and 23andMe. An FDA-funded study, which analyzed 61,401 tweets, demonstrated that 4,041 (7.2%) could be classified as proto-AEs (posts that resembled AEs), which was three times the amount typically reported to the FDA by patients.[24]

While the agency has been firm in addressing critical issues such as a balance in reporting benefits and risks of drugs, it also established a research partnership with PatientsLikeMe in June 2015 to help monitor AE reports from patients.[25] PatientsLikeMe has also partnered with UCB to create an online epilepsy community to track real-world experiences in dealing with the disease; the platform provides patients with an opportunity to directly report AEs to the FDA.[26]

Patient recruitment and social media

Today, 11% of clinical trials are leveraging social media for patient recruitment. Biogen Idec (now Biogen), for example, had been screening an average of six patients per week in its clinical studies. That rate reportedly shot up to 800 patients within two weeks of partnering with MyHealthTeam.[27] It was also interesting to note that as per a U.S. study on omni-channel recruitment outreach, apart from the benefit of significantly higher accrual speeds, it was found that the per-patient cost by direct mail was $30, versus 86 cents via the social media route.[28] In addition, the opportunity cost associated with a delay per day is significant. With 37% of sites failing to meet recruitment criteria and up to 10% not recruiting a single patient during a trial, the use of social media to rapidly and cost effectively scale up patient recruitment becomes key.[28]

The Mayo Clinic conducted a pilot study to demonstrate that social media can be effectively used to recruit large, demographically diverse patient groups in a cost-efficient manner, which served as a key message to HCPs.[29] A study of 1,516 randomly chosen tweets out of 15,346 that contained the phrase "lung cancer" demonstrated that about 18%

of the tweets were about clinical trials. Interestingly, only one of the tweets provided a link to a patient recruitment website.[30] With over 320 million monthly active users, Twitter could offer significant potential in driving patient recruitment.[13]

On the Facebook front, as the world progresses gradually toward virtual clinical trials, VERKKO, Sanofi's successful Phase IV trial for diabetes that evaluated a wireless blood glucose meter in a remote setting, recruited 60 patients, all online through Facebook. Interestingly, the average patient age was 56, with some patients older than 70; patient satisfaction scores were 4.52 out of 5, indicating that social media is not the domain of only the young.[31]

Crowdsourcing

Patient centricity continues to be an emerging theme in clinical research—and social media has been a key facilitator in this transformation. The dynamic between the two goes a step beyond reporting of AEs or patient recruitment, but also moves into the crowdsourcing of protocols. The first protocol to be crowdsourced with an investigational new drug approval was for Transparency Life Sciences' antihypertensive lisinopril.[32] Crowdsourcing was also used to assess the use of metformin in men with rising prostate-specific antigen after localized treatment for prostate cancer. Inputs were obtained from 43 physicians and 33 patients using Transparency's Protocol Builder platform. As patients would provide their feedback based on their own real-life experiences, it is expected that accrual rates would be much higher, since the real needs of the patient would be addressed. Protocols for irritable bowel disease, Parkinson's disease, and MS are also being developed using crowdsourcing.

The future

Where does pharma move from here? The biggest challenge the industry faces today is not that the value of social media is not well recognized or that the risk of AEs is deemed too high—it is how to reap the benefits of social media optimally. Clearly, the answer does not lie in listening alone, as most brands experience a steady state after listening for a while and no new incremental insights are observed. The industry's plain, vanilla social media services are not the answer; instead, the evolving trend is more toward digital services such as mobile apps that help track drug adherence, or more complex solutions like Amazon's Echo, a voice-enabled computer that can recite potentially lifesaving instructions for a user on say, for example, cardiopulmonary resuscitation during an emergency.[34]

The life sciences industry is also cognizant that today's informed patients and caregivers are looking for more credible information and better tactics of engagement than the traditional leaflets or, more recently, the occasional tweets. Engagement through online communities, health and fitness devices, and mobile apps is what the industry is looking at today.[35] Even traditional social media listening is moving into a new dimension, as pharma companies increasingly explore big data and natural language processing solutions and direct partnerships with forums such as PatientsLikeMe, with the two-pronged objective of (1) driving efficiency in the process and (2) getting real patient viewpoints.

Conclusions

The power of social media to transform healthcare is substantial. While the pharma industry has long suffered from social anxiety, it is increasingly opening up to the use of social media, and both HCPs and patients are becoming more cognizant of the power the communication tool wields. Watchful steps are being taken in this direction. When GSK recently conducted a search across Facebook and Twitter, the company found 21 million mentions of its products, and this data also resulted in the recall of one of its drugs. GSK worked with Epidemico to filter out irrelevant posts and to ensure compliance with FDA-reporting requirements.[36]

The industry is cognizant that today's informed patients and caregivers are looking for more credible information and better tactics of engagement than the traditional leaflets or, more recently, the occasional tweets.

While one may think that the cost implications are considerable and it would perhaps have been best if GSK would not have mined this data, the reality is that ADRs will be identified at some point of time, resulting potentially in more severe consequences for the manufacturer and significantly more harm for the patient population. Social media thus serves as a powerful enabler for responsible pharma companies that take ownership of patient safety, for patients who want to make informed decisions and share experiences, and for HCPs who want to engage with their patients and drive mutually agreeable decisions that are in the best interest of the patient. True patient centricity is not about ignoring commercial value, but about prioritizing the patient. Social media is the game changer in that equation.

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You've delivered great progress in the treatment and prevention of HIV in the three decades since its discovery, and slowed the rate of new infections in many countries. However, work continues in developing a safe and effective vaccine, a goal we've yet to reach due to the unique nature of the HIV-1 virus and the complex human dimensions of the infection, such as same-sex and mother-to-child transmission, the breadth of cultures involved and hard-to-treat patients. And while the use of PrEP and treatment as prevention has greatly reduced rates of transmission, its use has also had an impact on vaccine study design. You require new data, new insights and new expertise to deliver an effective HIV-1 vaccine, an indispensable component in the race to end HIV world-wide.

Join this webinar for a discussion of the progress you've made, the lessons learned, and the challenging road ahead in developing an HIV vaccine. We'll summarize recent advances in the immunopathology of HIV, encouraging new developments in vaccine research, the very limited status of pediatric studies, and why your work to develop a vaccine is more critical than ever to ending the pandemic.

Key take-aways:

- Clinical trial design is especially important to the success of your HIV-1 trial, and requires that you tap a high level of expertise and experience with clinical development plans and regulatory gap analysis.
- Allowing PrEP use in trial subjects may actually accelerate your HIV-1 vaccine trial.
- With a deep understanding of Human Data Science, you can use real-world data and evidence-based support to accelerate subject selection and more precisely target sites.

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

Mitigating Risk in Implementing Multi-Regional Trials in MS

Marie Trad, MD, Cathy Vanbelle, Benjamin Moody, PhD, Amy Del Medico, Olja Tanjga, MD, Sam Khinda, Lynne Hughes, PhD

Examining the main challenges in designing and executing MS clinical trials and proposing mitigation strategies that may help alleviate these burdens.

PEER REVIEW

Despite the market authorization of some 16 therapies for multiple sclerosis (MS), there is still no cure for this debilitating disease. In addition, all existing therapies pose safety issues, do not necessarily repair the damage caused by MS, may not have a robust effect on disability, and have not been proved to be effective in children, leaving significant unmet needs. MS is the most common cause of neurological disability in young adults, resulting in significant social and professional limitations for patients. Clinical trials of potential new therapies for MS have risen in number, particularly over the past decade, and are facing increased difficulties in identifying eligible patients. Many factors contribute to this issue, including the availability of approved therapies, exposure to previous therapies, and safety considerations, which together result in complex protocols that can be burdensome for patients. Yet, trials are needed if the therapeutic potential of new molecules in R&D to achieve a long-term improvement in disability is to be realized. Such compounds hold promise aimed at stopping damage to myelin and even boost remyelination. This article discusses the main challenges in implementing MS clinical trials and proposes mitigation strategies that clinicians may find helpful.

A brief introduction to MS and its therapy

MS, which is a chronic inflammatory disease of the central nervous system (CNS) that results in demyelination and axonal injury, is clinically characterized by recurrent and/or chronically progressive neurological dysfunction.[1] This disease affects some 2.3 million people worldwide,[2,3] around 75% of whom are women.[4] It is now widely accepted that MS involves an autoimmune process, involving an abnormal response by the immune system against the myelin in the CNS.[5,6]

Symptoms of MS tend to appear in young patients between the ages of 20 to 40 and are quite variable depending on the location and extent of the plaques in the central nervous system. Typical early symptoms are blurry or double vision, tingling, and loss of sensation. Motor dysfunction with limb weakness and spasticity, movement incoordination, and bladder and bowel dysfunction are also common symptoms of MS.

The causes of MS are not fully understood, but this disease is believed to involve a combination of factors:

- ***Immunologic***, involving an abnormal response of the body's immune system that is directed against the myelin in the central nervous system.
- ***Environmental***, including geography and, possibly, vitamin D deficiency.
- ***Infectious***, with a potential role of viruses in triggering the auto-immune cascade.
- ***Genetic*** association with the HLA-DR2 locus.[7]

Four clinical courses of MS were defined as a result of a scientific consensus in 1996: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS).[8] A revision of the above clinical forms was performed in 2013[9] and a new phenotypic classification was recommended to include clinically isolated syndromes (CIS) and exclude relapsing progressive forms with disease sub-classification as either active or non-active (with relapse and enhancing MRI lesions/T2 enlarging lesions). This classification includes:

- Relapsing forms: CIS and RRMS
- Progressive forms: primary and secondary progressive forms
- Gad T2 w T1 w

Therapeutic approaches to MS include relapse therapy, disease-modifying therapy (DMT), symptomatic therapy, alternative approaches, and rehabilitation. Tables 1, 2, and 3 on facing page provide a summary of DMTs, both injectable and oral, prescribed in RRMS clinical forms with their mechanism of action (MOA) and most common side effects.

Glance: Injectables

Drug name (first-line therapies)	MOA	Maximum dose	Comments
Interferon beta 1-a; Avonex I.M. Pegylated Avonex (Plegridy) (S.C.)	IFN-beta reduces antigen presentation and T-cell proliferation, alters cytokine and matrix metalloproteinase (MMP) expression, and restores supressor function	30 mcg once weekly IM 125 mcg IM injections once or twice a month	**Side effects are:** injection site disorders, flu-like symptoms, poor results on liver function tests, and blood cell abnormalities
Interferon beta 1-b; Rebif S.C. Betaseron Extavia S.C.		22 µg S.C. 3x per week 44 µg S.C. 3x per week RRMS: 0.25 mg (8 million units [1 mL]) every other day SPMS: 0.25 mg (8 million units [1 mL]) every other day	**Side effects are:** injection site disorders, flu-like symptoms, poor results on liver function tests, and blood cell abnormalities
Glatiramer acetate Copaxone S.C.	Complex immunomodulatory MOA combining induction of specific supressor cells of the T helper 2 (Th2) and increased IL-10 production through modulation of dendritic cells	40 mg once daily or 3x/weekly	Injection site reaction (possible ipoatrophy); rare systemic reaction with chest pain, dyspnea, and anxiety; infection; pain; nausea; arthralgia; hypertonia

Source: Trad et al.

Table 1. DMTs for MS (injectables intramuscular/subcutaneous).

Glance: Oral delivery

Drug name (first-line therapies)	MOA	Maximum dose	Comments
BG-12 – Dimethyl fumarate Tecfidera P.O.	Hypothesized to exert neuroprotective effects in patients with multiple sclerosis by activating Nrf2 transcriptional pathway	240 TID	**Warnings/precaution:** lymphopenia **Side effects:** Flushing, abdominal pain, diarrhea, and nausea
Terflunomide (Aubagio) P.O.	Has been demonstrated to selectively and reversibly inhibit dihydroorotate dehydrogenase, or DHODH, a key mitochondrial enzyme in the *de novo* pyrimidine synthesis pathway hence inhibiting T and B cell proliferation	7 or 14 mg/daily	The most common side effects are upper-respiratory-tract infections, urinary-tract infections, diarrhea, nausea, paraesthesia (pins and needles), alopecia (loss of hair) and increase in the liver enzyme alanine aminotransferase
Fingolimod (Gylenia) P.O.	Induces S1P1 down-regulation that prevents lymphocyte egress from lymhoid tissues, thereby reducing lymphocyte infiltration into the central nervous system (CNS)	0.5 mg PO qd	**Warnings:** decrease in heart rate and/or AV conduction; infection-increase risk, macular edema **Side effects:** headache, influenza, diarrhea, back pain, LFT increase

Source: Trad et al.

Table 2. DMTs for MS (oral therapy).

Overview of drug development in MS

Over the past two decades, 15 new therapies with a demonstrated effect on annualized relapse rate (ARR) have been approved and are available on the global market. Although most of these are injectable, since 2010, three oral therapies have been approved: Aubagio (teriflunomide), Gilenya (fingolimod), and Tecfidera (dimethyl fumarate). Of note is the May 2016 FDA approval of daclizumab for adults with relapsing forms of MS.[10] In addition, the FDA has recently approved ocrelizumab[11] for relapsing forms of MS and primary progressive MS.

Glance: Monoclonal antibodies

Drug name (second-line therapies)	Starting dose	Maximum dose	Comments
Natalizumab (Tysabri) infusion	Binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed tissue	300 mg infused over 1 hour every 4 weeks	**Warnings/ precaution:** PML **Side effects:** headache, fatigue, arthralgia, depression, abdominal discomfort
Daclizumab (Zynbrita) S.C.	Selectively binds to the high-affinity interleukin-2 receptor subunit (CD25)	150 mg once monthly	**Side effects:** increase in LFTs, skin reactions, hypersensitivity reactions
Ocrelizumab infusion	Anti-CD20	300 starting dose followed by 600 mg twice yearly	**Side effects:** infusion reaction
Alemtuzumab infusion	Targeting surface antigen CD52 leading to both T and B cell depletion	**2 treatment courses:** Course #1: 12 mg/day for 5 consecutive days Course #2: 12 mg/day for 3 consecutive days, 1 year later	**Side effects:** increased risk of malignancies, autoimmune disorders, life-threatening infusion reactions

Source: Trad et al.

Table 3. DMTs for MS (monoclonal antibodies).

Among major safety signals linked to MS therapies is the rare brain infection, progressive multifocal leucoencephalopathy (PML), which can have life-threatening and fatal outcomes.[12] Balancing the benefit/risk ratio is, therefore, especially crucial when prescribing any therapy for MS.

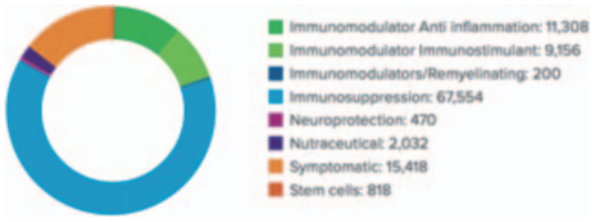
A wide range of companies, from small biotech firms to large pharmaceutical companies, are developing therapies for MS. Clinical trials in this therapeutic area tend to be complex and study objectives depend on the stage of clinical development. In Phase II studies, demonstrating reduction in cerebral lesion load using magnetic resonance imaging (MRI) is considered as a standard objective. While pivotal relapsing-remitting MS (RRMS) studies typically target a decrease in the ARR, there is now increasing interest in slowing the progression of disability, and in achieving no evidence of disease activity (NEDA). Most drugs under investigation for MS target the immunological system; very few candidates (~1% of those in development) have potential as remyelinating agents. In the real-world, late-phase environment, long-term safety data is being be collected.

The major drug categories in development are shown in Figures 1 and 2 on page 22.

Ongoing clinical trials in MS

The landscape for MS clinical trials has become increasingly competitive in the past five years (see Figure 3 on page 22), with 107,076 patients participating in almost 300 active clinical trials. Late-phase trials of marketed therapies account for 42% of all ongoing MS studies. The numbers of patients recruited to trials of various different MS drug candidates is illustrated in Figure 4 on page 22.

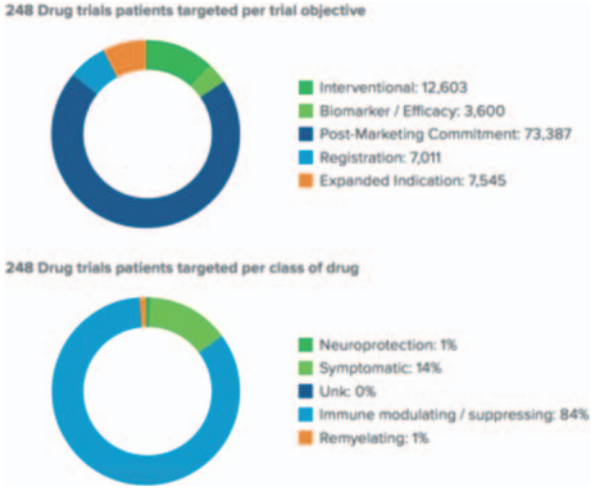
MS Clinical Distribution



Source: Trad et al.

Figure 1. MS therapies in development by category, with numbers of patients receiving each type of therapy.

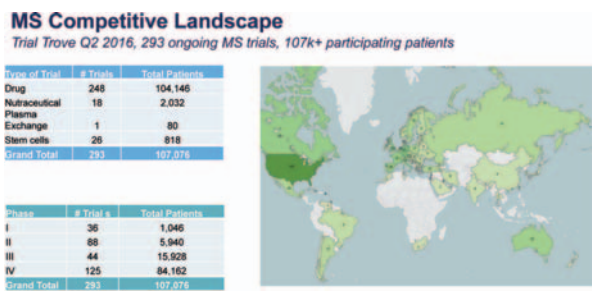
Trial Types and Targets



Source: Trad et al.

Figure 2. MS trials categorized by trial objective and class of drug.

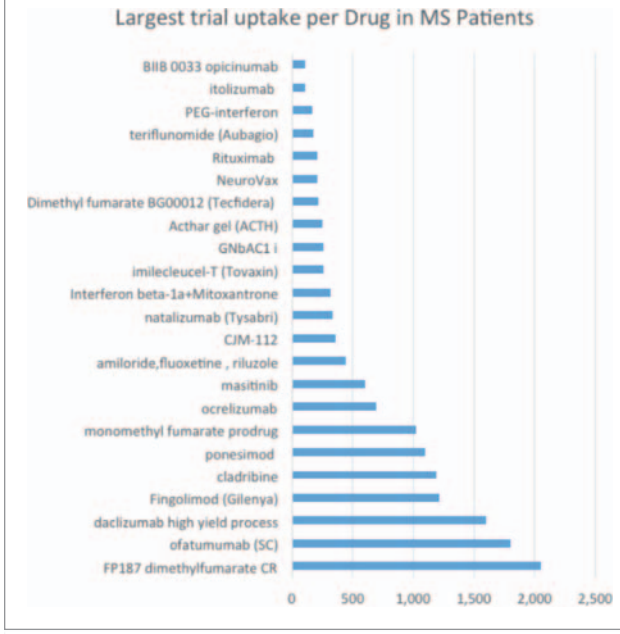
Crowded Field



Source: Trad et al.

Figure 3. The landscape for MS clinical trials.

Enrollment Ranges



Source: Trad et al.

Figure 4. Number of patients recruited to various MS drug trials.

Summary of experience gained and lessons learned

Methodology

Information from the QuintilesIMS (now IQVIA) global performance database summarizing historical trial metrics were analyzed, taking into account dates of initiation and end of recruitment, to obtain the most accurate recruitment figures at a site, country, and project level. Retrospective start-up metrics reflect the time it took to bring sites in any given country to a state of readiness to begin screening patients. In addition to regulatory and institutional review board (IRB) approval times, these also include the time taken to negotiate site contracts, perform site selection visits and ensure sites are provided with all the study-related supplies. Therapeutic expertise was also applied to the mentioned methodology, to accurately describe the current challenges observed in MS clinical trials.

Results

Based on historical data on experience with 76 MS trials performed at QuintilesIMS, involving more than 34,000 patients and 22 compounds in the last two decades, several important trends have been identified (see Figure 5 on facing page):

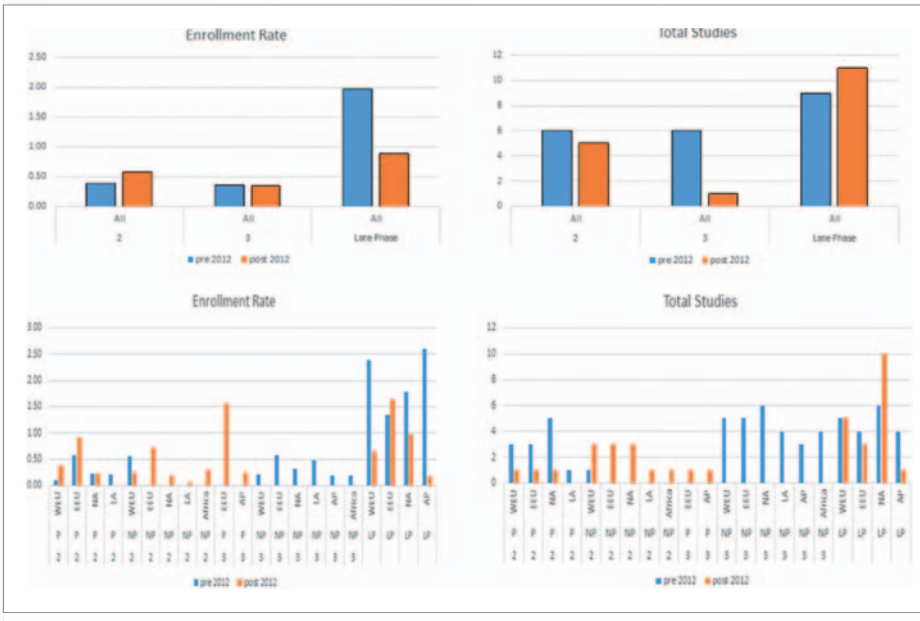
- ***A fall in overall recruitment rates***, particularly in late phase trials, and since 2012.
- ***A substantial increase in late-phase studies***, involving the 16 therapies that have completed mid-stage development, and most of which are on the market. There is also intense activity in development of entities with a unique mechanism of action.
- ***Shifting recruitment to Central and Eastern Europe*** over

the past five years, away from the traditional regions for clinical trials, such as Western Europe and North America. This shift is driven by difficult access to DMTs in Central and Eastern Europe. As a result, recruitment is also faster as patients more readily meet entry criteria relative to disease activity and limited exposure to other MS therapies.

- ***Decreased acceptance of placebo-controlled trials***, although in some regions this is still acceptable if limited to six months or less.

These trends are based on an analysis of the 76 clinical trials performed by QuintilesIMS between 2000 and 2016, excluding trials that were ongoing, Phase I, discontinued, or involved symptomatic therapy (gait, balance, cognition, relapse, spasticity). Of the 38 remaining studies, 10 were Phase II studies with a placebo arm (six studies) and without placebo (four studies); seven were Phase III studies, all without a placebo arm except for one study performed in Asia; and 21 were late-phase studies, of which seven were Phase IIIb, 10 were interventional, and four were observational Phase IV studies.

Case Study: Recruitment Trends



Source: Trad et al.

Figure 5. Recruitment patterns in QuintilesIMS MS studies.

> There has been an overall reduction in relapse rates, due to previous exposure to multiple MS therapies, making it hard to find suitable study participants.

Mitigation strategies

Based on QuintilesIMS experience in performing large MS programs, recruitment challenges necessitate specific mitigation plans. Several factors appear to have an effect on recruitment to MS trials, as described ahead.[13,14] Specific mitigations strategies that were put in place to enhance recruitment, reduce drop-out rates, and accelerate completion of timelines included:

1. ***Protocol design and study entry criteria***: Placebo-controlled clinical studies are becoming less acceptable, even for studies with short durations. Long washout periods of previous MS therapies affects recruitment significantly. Also, there has been an overall reduction in relapse rates,[15] due to previous exposure to multiple MS therapies, making it hard to find suitable study participants.
   - ***Mitigation strategies:***
     - Simplify protocols, and limit studies with placebo arms.
     - Consider allowing first-line therapies up to the randomization visit, especially in studies of long duration.
     - Anticipate the potential effect of protocol amendments on the ability to recruit "real-world" patients.
     - Site selection visits (SSVs) need to be comprehensive to make sure the site has the right equipment with access to an MRI facility, resources to conduct the scales, patient-reported outcomes (PRO) training), and is fully engaged with the protocol.
2. ***Burden of participation for patients***: This depends on the frequency and duration of clinical visits. Trials may involve invasive procedures such as lumbar punctures; if mandatory, this poses a significant hurdle for recruitment. There may be a requirement for hospitalizations or safety observation after administration of the investigational product, as well as a prolonged washout of previous therapies and prohibited medications.
   - ***Mitigation strategies:***
     - Simplify the study schedule and reduce the patient burden by minimizing assessments and decreasing the need for PROs, especially in early-stage development.
     - Allow for optional cerebrospinal fluid collection rather than mandatory lumbar punctures.
     - The relationship between the patient and site is key to retention, so tools to foster this relationship can encourage patients to stay engaged throughout the duration of the study.
     - Recruitment tools should be tailored for countries and sites, and may be patient-facing (study educational materials in the form of videos, pamphlets, posters, flyers or letters

from a physician to patients), site-facing (also including study educational materials and a pre-identification website), or for advertising and outreach (including digital, radio, and print media outreach; contact with MS support and advocacy groups; and local meetings).

3. ***The clinical form of MS involved***: The RRMS arena is highly saturated and extremely competitive. Although PPMS is less saturated, the low prevalence and increasing competitive studies have a growing effect on available participants in clinical trials. Pediatric MS clinical trials are also challenging to complete, mainly because of a low prevalence and complexity inherent to this population.
   - ***Mitigation strategies:***
     - Select specialized high-performing centers based on previous experience (recruitment, quality), offering support with additional resources if required.
     - Studies should be implemented in regions where patients have higher disease activity because of low exposure to DMTs.[16]
4. ***Therapy-related factors***: These include the mechanism of action of the compound, with DMTs and remyelinating agents garnering more scientific and medical interest than symptomatic therapies; and the mode of administration, with oral formulations accepted more readily by patients than injectable ones. Other factors are the availability of approved treatment options and of alternative clinical trials with additional elements, along with availability of therapy after the study.
   - ***Mitigation strategies:***
     - Provide for long-term availability of investigational product, especially in countries where MS therapies are not easily available.
     - Permit higher levels of participation by Eastern and Central European sites by avoiding caps on recruitment per site and per region.
     - Explore new countries and regions (Asia, United Arab Emirates, Kuwait, Lebanon); even if these have a lower prevalence of disease, this is balanced by a lower exposure to clinical trials.
     - Consider allowing use of certain DMTs—such as interferons—until randomization, avoiding the need for washout during the screening period, especially if the active control is an interferon.
     - Provide comparator where applicable.
     - Plan for targeted Investigator engagement to discuss the science and any unique mechanisms of action (MOA) of the investigational product.

Conclusion

Recruitment in MS clinical trials is becoming increasingly challenging. This was confirmed by the analysis of the trials performed at QuintilesIMS, revealing a decrease in recruitment, mainly in late-phase interventional studies. Similar trends already have been observed in other MS studies.[15] Early implementation of specific mitigation plans and strategies described in the article are needed to allow study completion within predefined timelines. In addition, technological advances will be helpful, including the potential for electronic medical records (EMRs) and prescription data to be used to expedite recruitment.

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Dermatology Biologics: Overcoming Challenges to Fulfill Therapeutic Potential

Compared to small-molecule systemic therapies, biologics are usually associated with fewer adverse events because they tend to focus on specific processes and do not have sweeping effects throughout the whole body.

Darcee Strube
Senior Vice President,
Dermatology Division,
Novella Clinical

Biologics have gained a foothold in dermatology, and growth in this area has been fueled by improving clinical outcomes. The dermatology market is expected to grow to $33.7 billion by 2022, and 37% of drugs currently in the pipeline in this segment are biologics, according to a 2016 report by GBI Research. These drugs, as well as recently approved products, address such conditions as moderate-to-severe plaque psoriasis, atopic dermatitis, hidradenitis suppurativa, urticaria, and alopecia areata. To be a prominent player in the market for dermatologic therapies, companies developing biologics must successfully navigate a series of significant challenges, including patient compliance, medication costs, and patient safety.

Compliance

Biologics are typically a third-line treatment option for patients who have not responded sufficiently to topicals and/or phototherapy. However, issues with patient compliance may prevent patients from receiving the full benefits of therapy. Patient compliance is impacted by how drug regimens are administered, e.g., a self-administered injection vs. in-clinic intravenous infusions. Frequency, dosage, need for monitoring, and safety concerns can also influence overall compliance. Noncompliance with treatment regimens may lead to adverse effects such as the formation of anti-drug antibodies. To help ensure patient compliance for dermatology treatments, patient advocacy groups recommend a focus on goal setting. The National Psoriasis Foundation's "Treat 2 Target" program provides a set of treatment goals for patients to use with their providers. The goals, published online in the *Journal of the American Academy of Dermatology* in November 2016, include doctor visits at three and six months after initial diagnosis or the start of new treatment to monitor progress with a target of 1% or less of psoriasis covering the body.

Quality of life vs. medication costs

Biologics can be more effective than topical therapies because they address underlying disease and inflammatory mechanisms rather than merely the symptoms. This has led to noteworthy improvements in patient outcomes, as outlined in a 2014 study which examined quality of life and mental health in psoriasis patients comparing biologic treatments to other modalities. The study concluded that patients treated with biologics saw a 52.2% decrease in General Health Questionnaire (GHQ-30) scores, as compared to a 24% and 17% decrease among systemic and topical treatments, respectively. This data suggests biologics may lead to better outcomes for some psoriasis patients. Valeant Pharmaceutical's brodalumab (Siliq) is reportedly the first product to demonstrate 100% improvement in the psoriasis area and severity index (PASI 100) as a primary endpoint in clinical trials. Furthermore, biologics have the potential to improve patient quality of life beyond the treatment paradigm, including lower levels of anxiety, social dysfunction, sleep disturbance, and somatic symptoms.

However, the cost of biologics is rising, and they are typically more expensive than oral systemic therapies. Yet there is some positive news: A study published in the *British Journal of Dermatology* found biologics that treat moderate-to-severe plaque psoriasis reduce costs associated with major changes in the pattern of healthcare delivery, reduce the number of inpatient admissions by more than half, and reduce the mean number of inpatient days by more than 75%.

Safety

Due to rare but potentially serious side effects, patient safety is a major consideration in biologics trials compared to studies of other dermatologic agents. Now, the level of oversight is greater, safety monitoring is more frequent, and safety teams, usually small for dermatology studies, have become much larger. In clinical trials, detailed inclusion/exclusion criteria are strictly enforced to protect patients. While further research is needed, dermatology patients and physicians still welcome the overall benefits and safety profiles of biologic treatments. Patients are experiencing greater skin clearance and quality of life than ever before.