Volume 24 Number 4/5 April/May 2015

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Volume 24 Number 4/5 April/May 2015

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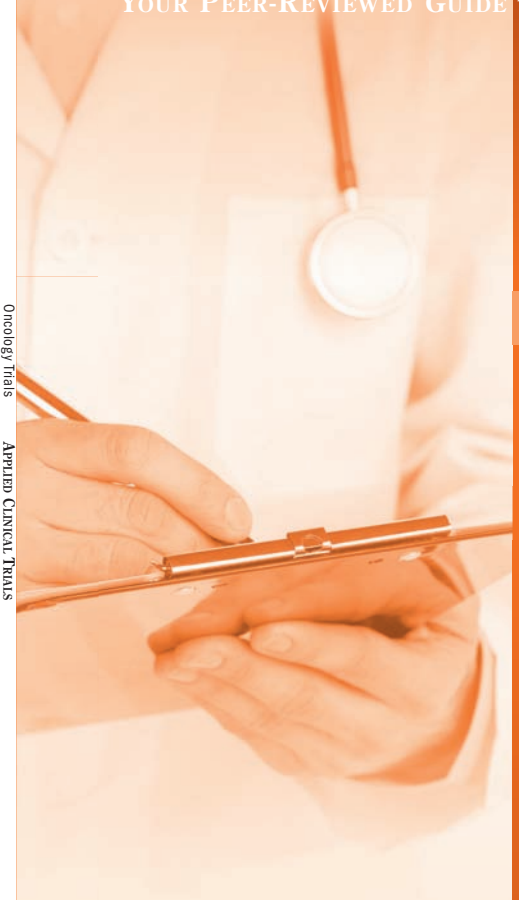

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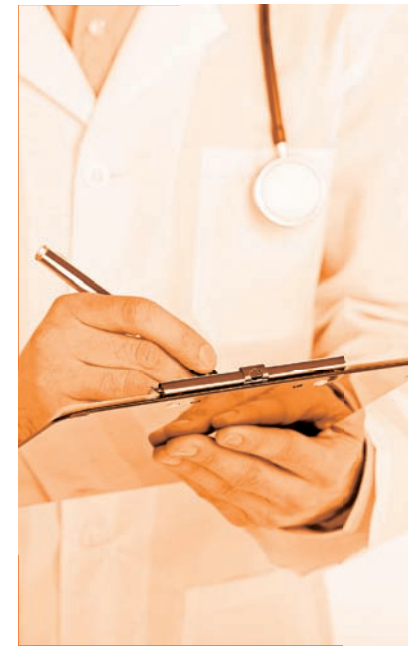
APPLIED CLINICAL TRIALS (Print ISSN: 1064-8542, Digital ISSN: 2150-623X) is published 6 times a year as combined issues in Feb/March, Apr/May, Jun/July, Aug/Sept, Oct/Nov, Dec/Jan by UBM Advanstar 131 West 1st Street, Duluth, MN 55802-2065. Subscription rates: $70 for 1 year (12 issues), $120 for 2 years (24 issues) in the United States and possessions; $90 for 1 year, $140 for 2 years in Canada and Mexico; all other countries $130 for 1 year, $235 for 2 years. Single copies (prepaid only): $9 in the United States and possessions; $11 in all other countries. Add $6.50 per order for shipping and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to *APPLIED CLINICAL TRIALS*, P.O. Box 6115, Duluth, MN 55806-6115. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

APPLIED CLINICAL TRIALS

VOLUME 24, NUMBER 4/5



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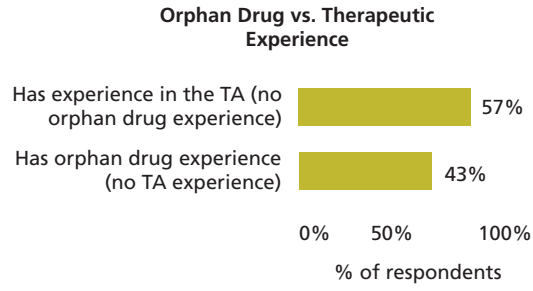
Sponsors, Which CRO Would You Choose for Orphan Drug Development?



Source: Industry Standard Research, February 2015

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eBooks

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Sentiment Analysis: Understand Your Healthcare Customers

Sentiment analysis can give healthcare companies a competitive edge in understanding what customers think about their healthcare experience, to help reduce costs and improve care service, and to lead to new clinical research and treatments. It also taps into a new channel of pharmacovigilance input information that can enable marketing authorization holders to keep abreast of opinions on the safety of their products in real time.

In the context of drugs and devices, sentiment can be referred to an adverse event experience but also a positive treatment outcome. The sentiment can be deducted as final output of a technique that includes the massive collection of some unstructured information from any source selected as relevant and their processing aimed to identify and extract the implicit subjective judgment or evaluation.

The main goal of the proof of concept (PoC) is to show the applicability of a sentiment analysis approach to clinical data, in the context of social media monitoring, data analysis, and reporting. This POC focuses on sentiment analysis of opinions shared on the Web about two products for melanoma: Roche's Zelboraf and GlaxoSmithKline's combination of Mekinist and Tafinlar. The study gathered user comments from three different types of data sources—online patient fora, Facebook public fan pages, and Twitter, where tweets were collected daily for a one-month period.

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Public Opinion Matters—And Merits Attention

Media rebuke of Europe's Innovative Medicines Initiative thrusts debate into the public arena

This spring, the European Union (EU) will hold a high-level conference with a wide audience including public and patient representatives, with the aim of improving vaccination coverage rates and promoting general reflection on the value of vaccination. Alarming outbreaks of communicable and eminently preventable disease are jolting health authorities across Europe into the realization that public understanding is a vital part of any health policy.

The European Centre for Disease Prevention and Control says that "the root cause of the continued measles and rubella transmission in the EU is the sub-optimal uptake of MMR vaccine, leading to an accumulation of susceptible individuals." It estimates that 4.9 million children born between 1998 and 2008 missed the first dose of measles vaccine, and the number of children who did not receive a second dose is even higher.

John Ryan, a senior health official in the European Commission, recently acknowledged that "there is insufficient understanding of the value of immunization, both among healthcare workers and the general public. Inaccurate perception of the safety and effectiveness of vaccines, on the one hand, and underestimated risks of communicable diseases, on the other hand, result in vaccine hesitancy in the general public." And no less a figure that Guido Rasi, until recently the executive director of the European Medicines Agency (EMA), remarked at a recent meeting on the subject: "Important issues have been raised by civil society in terms of advocacy of vaccines; the voice of patients and civil society is the most powerful, and one of the few credible today."

The recognition of the importance of public opinion in Europe has implications that go far beyond the realm of vaccines. And one of the implications is that in other areas of health—and notably in terms of medicines development—the attention to public opinion also needs to be sharp. An intriguing test arose in March when three respected European news organizations—Der Spiegel in Germany, De Standaard in Belgium, and the Swiss public broadcaster SRG SSR—produced an extensive critique of the EU's biggest drug research program, the Innovative Medicines Initiative (IMI). The essence of the report was a suggestion that public money is subsidizing private-sector research, and that inadequate controls over the program were leaving the interests of patients, academics, and smaller companies sidelined in favor of big pharma.

Peter O'Donnell
is a freelance journalist who specializes in European health affairs and is based in Brussels, Belgium.

Direct accusations

The accusations were direct—and naturally attracted considerable public attention. With headlines such as "Europe pampers the drug industry," "No control over individual drug firms," "No real transparency," "IMI ignores WHO priorities," or "Patients are turned into drug industry lobbyists," the interest of readers and viewers was naturally provoked. But what proved as interesting as the accusations themselves was the way the discussion then evolved in Europe among the organizations involved. I take no sides in the debate—both because it is not my role as a journalist to take sides, and also because I declare a tenuous interest in the subject: I am an (unpaid and entirely independent) member of the advisory board of one of the IMI projects impugned, the European Patients Academy. I restrict myself here simply to summarizing the arguments and counter-arguments that ensued.

The critics asserted that the research agenda pursued by IMI (into which the EU put €2.6 billion—close to $300 billion over the last five years) has been dominated by private companies hungry to replace diminishing blockbuster profits by grabbing public money to pay for their development projects. As a result, the projects reflect industry interests in profitable product segments rather than the therapeutic areas listed as priorities by the World Health Organization (WHO). Academics and smaller companies have experienced difficulty in access grant money from the complex, secretive, and highly competitive tendering procedures. Intellectual property protection arrangements are opaque and biased towards industry interests, and subsidized trials are unethical and focus more on the profitable U.S. market than on

European needs. In addition, there is insufficient access to details of just what industry is contributing, and lack of transparency leaves scope for conflicts of interest.

The accusations were substantiated by reference to named sources: a Dutch professor, one former and two current members of the European Parliament, some German biotech companies, some university associations, a renowned Italian investigator, a German advisory body, and a member of the advisory board of the patient academy.

A rapid reaction

The drug industry reacted swiftly, with a statement from the European Federation of Pharmaceutical Industries and Associations, issued the day after the accusations were published. It offered some general justifications for IMI as a "platform through which the pharmaceutical industry, academia, and regulators may collaborate to find suitable solutions" to "significant challenges" Europe faces of "providing effective and timely treatment to its citizens." It pointed out that pharmaceutical companies do not receive any direct financing for their input, and commit their own resources to IMI projects. (The principle of IMI is that contributions are made in kind by participating companies—for instance, in terms of their researchers' time—to match the EU grant money.) It claimed that the research agenda is "aligned with the 2013 update of the WHO's Priority Medicines for Europe and the World Report," and that the intellectual property rules "apply equally to all public and private partners." And it listed the mechanisms for certifying and verifying companies' reports of their contributions.

But it made no mention of complaints from academics and smaller companies about difficulties in access grant money, or about the alleged complexity and secrecy and competitive nature of the tendering procedures. Nor did it respond to accusations of unethical trial procedures, undue focus on the US market, or potential for conflicts of interest.

General justification

Three days later, IMI issued its own statement, which also offered some general justification for the program. It specified that "large pharmaceutical companies do not receive any IMI funding," that most grant recipients are academics, that smaller firms receive 17% of funding, and that "patient groups and regulators are also well represented." Through the intellectual property protection policy," project partners are sharing compounds, data, and knowledge with one another in an unprecedented way, in an open innovation ecosystem." IMI governance is shared between EFPIA and the European Commission, and input comes from its scientific committee and from EU member countries, and it is "scrutinized closely by other EU institutions including the European Parliament." Most project ideas come from EFPIA companies, but "other organizations can also put forward ideas."

Again, it left some of the accusations unanswered—and the case for the defense immediately provoked further criticism from healthcare campaigners. Citing a (subsequently-deleted) passage from the EFPIA website, Helle Agaard of MSF said: "To use EFPIA's own words, the Innovative Medicines Initiative offers pharmaceutical companies 'tremendous costs savings' when taxpayer money is used to pay for research that companies would otherwise have to do themselves. That in itself is a dubious practice. What makes it worse is that these subsidies come with no strings attached to ensure that final medicines, vaccines, and diagnostics are affordable to the public afterwards, or that the research is driven by where the biggest public health need is."

Tessel Mellema, a policy advisor with Health Action International, said: "The intellectual property principles published on the IMI website are very general. Without more detailed information about the deals that the industry negotiates, it's impossible to tell whether taxpayers are getting a good deal. More importantly, these principles don't say anything about affordability of the end products developed using IMI money." It took another two days for more specific answers to be offered by IMI, EFPIA, and the European Commission to the detailed accusations.

> **The essence of the report was a suggestion that public money is subsidizing private-sector research, and that inadequate controls over the program were leaving the interests of patients, academics, and smaller companies sidelined in favor of big pharma.**

Everyone will draw their own conclusions from this debate. One inescapable conclusion, however, is that the level of debate might be higher, and interventions might be faster and more specific. Since this type of debate is taking place in the public arena, its conduct as well as its content will influence public opinion. The logic therefore demands that anyone—or any organization—claiming to have the public interest at heart must be more attentive to the quality of public debate, and to their input to it.

Front & Center

Adherence-Informed Clinical Trials to Optimize Drug Development

Electronic measurement and analysis of medication adherence addresses the greatest source of variability in drug response

The drug approval process is based on a key assumption: patients in clinical trials are reliably adherent to the dosing regimen specified in the protocol, and are thus optimally exposed to the test drug(s).

The reality has proven to be strikingly different. "Patient adherence in drug trials, like patient adherence in real world settings, varies tremendously," said Bernard Vrijens, PhD, Chief Science Officer, MWV Healthcare. "But if you don't measure and reliably evaluate adherence, you don't recognize deviations in drug exposure, and you cannot adequately and accurately explain trial results. We can no longer afford to ignore adherence."

When adherence is not monitored or is unreliably measured, it is generally assumed that adherence is nearly ideal in clinical trials. This view, however, is contradicted by extensive evidence provided by reliable electronic methods of measurement. Results from these methods, reported in nearly 700 peer-reviewed publications and cited over 47,000 times, show that suboptimal adherence is prevalent in ambulatory trials, in which outpatients are responsible for taking the drug according to the protocol-specified dosing regimen.

Pill counts are one of the earliest and longest-used methods to assess patient adherence. Despite the fact that returned tablet counts have repeatedly been proven to overestimate adherence because of prevalent discarding of untaken tablets, pill counts continue to be used as an adherence measurement, in addition to regulatory use for drug accountability in trials. Patient self-report

Bernard Vrijens

is affected by recall and desirability bias and is the second most frequent measure of adherence in trials.

The persistent use of inadequate or nonexistent adherence measurements in trials has created the following problems: failed treatment; inappropriate dose escalation; overestimated dosing requirements; emergence of drug-resistant microorganisms during anti-infective drug trials; hazardous rebound or first-dose effects; misdiagnosis when drug response is a diagnostic criterion; underestimated efficacy of the test agent; type 2 errors in judging efficacy; underestimated incidence of dose-dependent adverse effects; and distorted pharmacoeconomic analyses.

Trial sponsors who replace assumptions about adherence with reliably measured adherence data achieve more robust, more reliable and more actionable results. The effectiveness of pre-exposure prophylaxis for the prevention of HIV infection, for example, is highly dependent on adherence. Trial data for the leading pre-exposure prophylactic agent showed less than 50 percent efficacy until adherence data was evaluated. A subgroup analysis showed 100 percent efficacy and more than 95 percent adherence when using MWV's Medication Event Monitoring System (MEMS™), which monitors, measures and analyzes patient adherence for real-time adherence-based adjustments during the trial. In this example, reliable data analysis was instrumental in transforming trial failure into successful product approval.

The MEMS system utilizes "smart" packaging that electronically tracks medication-taking behavior and wirelessly transfers the data to a state-of-the-art, statistical analysis system. The MEMSCap can be fitted to any standard drug container. Today, smart packaging is available for monitoring adherence with different form factors, including blister packaging, injectable medications, and inhalers.

MEMS was created to measure and manage adherence in clinical trials. The primary objective of using MEMS in drug development is to get the best possible estimate of efficacy and safety, and finally the best possible pricing, strictly based on objective measures. The effectiveness of certain hepatitis C medications, oncology treatments, anticoagulants and other narrow therapeutic index agents is intimately related to adherence. Monitoring adherence, including the time of dosing, provides clinicians and sponsors with a true, evidence-based picture of dose-dependent drug response, adds efficacy data, helps to identify the appropriate dose, and underlines the need for adherence to achieve

> Patient adherence in drug trials, like patient adherence in real world settings, varies tremendously," said Bernard Vrijens. "But if you don't measure and reliably evaluate adherence, you don't recognize deviations in drug exposure and you cannot adequately and accurately explain trial results. We can no longer afford to ignore adherence.

effective treatment in clinical use. Adherence-informed trials using MEMS are an effective vehicle for moving through the drug approval process.

The pharmaceutical industry recognizes that adherence generally declines over time in clinical practice. Similar declines in adherence in clinical trials have largely been ignored. Under-dosing, the most common form of non-adherence, simultaneously decreases the effect size and increases the variation in effect, which in turn weakens statistical power to the extent that proof of efficacy cannot be established. The drug candidate often fails because of lack of efficacy resulting from patient non-adherence to the test drugs.

Some study protocols attempt to compensate for non-adherence by increasing the specified dosage(s). Higher dosing may induce unacceptable toxicities in adherent patients, leading to a safety profile that overstates the potential for adverse events. Elevated adverse event rates are a leading reason promising drug candidates fail the trial process.

Adherence data becomes increasingly important as drug development focuses on targeted therapies with narrow therapeutic indices, in which the drug response is both dose and time dependent. Depending on the half-life of an agent and the therapeutic index, the timing of a dose can be as important as whether or not the dose was taken.

Adherence is a three-part process—initiation of treatment, implementation of the dosing regime, and eventually discontinuation.

In clinical practice, *initiation* is the key barrier. On average, 20 percent of patients never pick up their initial prescription. Patients in clinical trials, however, are highly selected and have given informed consent. Trial participants sometimes have higher motivation to *initiate* treatment than in routine care.

But once the trial begins, participants tend to revert to daily routines, and *implementation* is impacted. They forget doses. They get too busy to take a dose. They are uncomfortable with side effects, real or perceived, and take a drug holiday or stop treatment entirely. And like patients in clinical practice, patients in trials typically fail to mention their lapses to trial staff.

Unfortunately, trial analyses are based usually on the intention to treat, a methodology that assumes perfect adherence to protocol. Dose-ranging studies, safety and adverse event profiles, equivalence studies, comparisons with active controls and most other outcome results are based on an underlying assumption of perfect adherence. Poor adherence skews trial results toward failure.

Regulators recognize the problems that non-adherence brings to trials. In 2012, the U.S. Food and Drug Administration (FDA) issued draft guidance on "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products." FDA called on trial sponsors to decrease heterogeneity by first identifying and selecting patients who are likely to adhere to the dosing regimen as specified in the protocol and second, by boosting adherence through the use of smart packaging that monitors drug use during the trial so patients can be encouraged to be more adherent.

Adherence is a behavior that can be learned, encouraged and reinforced by habits. Prompt feedback and education can increase adherence by 20 percent or more in individual patients.

This enhanced adherence can help optimize drug response and reduce residual variation to increase the statistical power of the trial. Adding adherence monitoring to a trial protocol can do more to increase the statistical power of a study than simply increasing patient numbers with the same unknown variability in adherence.

"You cannot predict adherence, but you can measure it," Vrijens said. "When you measure adherence, you can manage it to reduce its negative impact on efficacy and safety. Adherence-informed drug trials give you more robust, more reliable and more actionable data."

Reference topic: http://goo.gl/6Z4qlH

For more information on this research, please reference: Vrijens B, Urquhart J. Methods for Measuring, Enhancing, and Accounting for Medication Adherence in Clinical Trials. *Clinical Pharmacology and Therapeutics*. 2014. 95(6): 617–626

VIEW FROM WASHINGTON

Congress, White House Seek to Spur Biomedical Innovation

The productivity and efficiency of the U.S. biomedical research enterprise is undergoing a broad re-examination that includes assessment of how FDA regulation serves to bring—or block—new medicines from the market. FDA policies for developing new medical technology are considered in President Obama's "Precision Medicine Initiative," a $215 million program to create a massive database of patient genomic information to stimulate biomedical research. While the program focuses on initiatives by the National Institutes of Health (NIH) to identify genomic factors important in developing effective treatments for cancer and other diseases, FDA is charged with devising strategies that will encourage innovation related to next generation sequencing (NGS) technologies.

FDA recognizes the importance of NGS systems for identifying critical genetic variants, but also wants to assure that tests are accurate, reliable, and clinically relevant. Access to broader patient genomic information promises to help identify individuals for targeted clinical trials, along with other techniques for evaluating new therapies for cancer and other serious conditions. The National Cancer Institute (NCI) is examining how genomics data could enable an "open clinical trials" system that enrolls patients who share targeted genetic lesions.

FDA examined strategies for regulating how NGS diagnostic tests should demonstrate analytic validity at a public workshop in February and in a discussion draft on the topic. The agency has approved limited "carrier" tests that screen for specific gene variants. A sign of increased regulatory flexibility is its recent approval of 23andMe's test for the rare Bloom syndrome under a streamlined review process, which may provide a model for authorizing additional NGS products.

Congressional incentives

Multiple proposals for revising FDA policies are included in the "21st Century Cures Act," a massive document unveiled in January by the House Energy & Commerce Committee. The package features patent and exclusivity provisions to encourage private sector investment in biomedical research and antibiotic development, along with measures to streamline clinical trial operations and reform oversight of medical devices.

Similarly, the Senate Health, Education, Labor and Pensions (HELP) Committee is examining FDA and NIH policies related to biomedical innovation, starting with a lengthy report from Republicans on FDA regulatory inefficiencies and outdated policies accused of delaying medical product development. The HELP panel launched a broad review of these issues last month with a hearing to gain input from NIH director Francis Collins and FDA commissioner Margaret Hamburg, probably her last appearance on Capitol Hill as FDA's leader. Hamburg announced in February that she would leave FDA at the end of March after six years on the job. Chief scientist Stephen Ostroff heads the agency pending action in the White House and Senate to nominate and confirm a new commissioner.

Meanwhile, enactment of any FDA reforms this year requires fast consensus on a few specific measures agreeable to both sides of the aisle, such as incentives for testing new antibiotics. Otherwise further FDA reform legislation will wait until 2016, when Congress will face a hard deadline in 2017 for authorizing the next round of FDA user fees.

Regulatory responses

Many of the Congressional provisions for stimulating biomedical R&D are not new and already are being implemented by FDA. For example, the agency stole the thunder from a House compassionate access proposal by unveiling in February a shorter and simpler form for physicians to seek access to investigational drugs for individual patients. Compassionate use advocates still criticized the change as "window dressing," but the FDA guidance appears to have softened charges that excess government regulation blocks patients from critical therapies.

FDA officials would like to do more to support development of biomarkers and innovative clinical research strategies, and additional resources would bolster such efforts. The Obama administration has proposed a small increase in FDA funding for 2016, but most new dollars for drugs and biologics comes from higher user fees. FDA officials thus are very wary of new legislation requiring additional reports and rules and creating new oversight programs—but without added money to finance those efforts.

Agency critics looking to streamline rules governing drug development and testing may be interested in the agency's latest calculation of the time spent by sponsors and investigators to comply with all the requirements for submitting forms and keeping records related to investigational new drug (IND) applications. The small print in a recent FDA Federal Register notice (March 3, 2015) indicates that IND reporting and recordkeeping for drugs and biologics adds up to 23 million hours a year. Submitting an IND for an investigational drug averages 1,600 hours—and with 2,600 "responses," that totals more than four million hours. An IND protocol amendment involves only 284 hours to submit, but there are more than 20,000 of them and thus requires more than six million hours to complete them all.

— Jill Wechsler


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GLOBAL REPORT

EFGCP Issues Roadmap on Medical Devices

The MedTech Europe Medical Technologies Working Party of the European Forum for Good Clinical Practice (EFGCP) has produced a roadmap that is designed to boost understanding of medical device development in Europe.

This initiative is aimed at answering the central question of what constitutes a high quality of clinical evidence for medical technology, in particular from an ethical, patient, clinical, and regulatory perspectives.

"New regulations under consideration in the EU focus on new technologies such as novel *in vitro* diagnostics (IVDs), companion diagnostics, and on the development of healthcare apps, all of which rely on information to deliver positive health outcomes," noted the EFGCP in a statement. "Gathering clinical evidence and knowing when and how to conduct clinical investigations for these new technologies is a challenge which still needs to be addressed."

The Working Party is determined to address these open questions and investigate the generation of clinical evidence for IVDs, companion diagnostics, and healthcare apps from the point of view of clinicians, patients, regulators, and product developers. To start the process, it is organizing a multi-stakeholder workshop on establishing best practices in clinical development of devices in this area. Called "Barriers and Pathways to Success," the event will take place in Belgrade, Serbia, May 7-8 at the Chamber of Commerce and Industry of Serbia.

This will be followed by a two-day workshop on "Ethics, Quality and Oversight in the Clinical Development of Medical Devices," to be held at University College London June 15-16. The Working Party is organizing another workshop on risk management and regulation at the Central Hospital of Luxembourg in October, and then a roundtable on combination drug/device products in Leiden, Netherlands, in January 2016. "A constructive and energetic year is planned, to make sure the medical technology sector has its own spotlight and that concrete solutions are found for the well-being of patients," said EFGCP chair Ingrid Klingmann, MD.

For more information, visit www.efgcp.eu.

— *Philip Ward*

DATA ANALYSIS

Adaptive Trial Designs Gaining Momentum

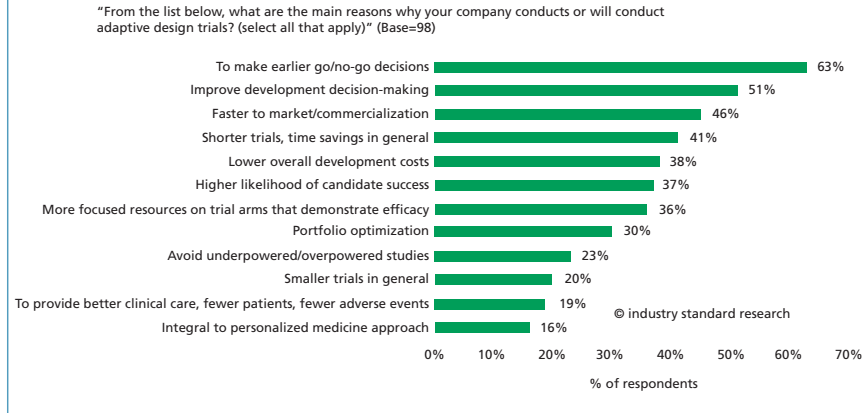
In ISR's 2015 Adaptive Trials: Market Dynamics and Service Provider Benchmarking report, a key takeaway reached is that the primary driver of adoption of adaptive designs is the ability to reach critical decision points earlier. This does not necessarily mean that trial timelines are shorter or costs are lower, but instead that the probable outcomes of these trials are determined earlier so resources can be more effectively allocated to more promising or profitable drugs or devices. ISR found this as a chief motivator for the continued growth of adaptive trial designs. While only 49% of respondents report that they are currently conducting a trial with an adaptive design, 82% anticipate they will be over the next 12 months.

When ISR asked respondents what their main reasons were for conducting trials with adaptive designs, 63% said to make earlier go/no-go decisions.

The primary hesitation associated with using adaptive trial designs relates to the regulatory environment surrounding adaptive trials. Upwards of 60% of ISR's survey respondents perceived adaptive trials as at least "somewhat risky."

— *Industry Standard Research* (ISR)

Faster Go/No-Go Decisions the Top Driver



Source: ISR's 2015 Adaptive Trials: Market Dynamics and Service Provider Benchmarking report

REGULATORY REFORM

FDA, Sponsors Look to Expand Patient Input to Clinical Trials

Patient focused drug development (PFDD) is moving into the mainstream, promising to alter the conduct of clinical trials and FDA regulatory policies. PFDD appears increasingly useful and accepted in designing studies and in assessing outcomes and treatment benefits most important to patients with a certain condition. Building on the experience gained from a series of FDA meetings to solicit patient perspectives for treating chronic conditions, sponsors are querying patient groups to help define the key goals of clinical studies and to avoid research programs that yield less useful results. FDA is bringing in patients to consult with review divisions and to join FDA-sponsor meetings to help shape research studies and product labeling.

To further this trend, FDA is expanding its patient representative program beyond participation in advisory committee meetings. The agency has identified some 200 patient representatives based on their experience, FDA training, and clearance on conflicts of interest. Last year, members of this cadre were involved in 10 consultations with FDA review divisions and in additional meetings with sponsors, explained Richard Klein, head of FDA's patient liaison program in the Office of Health and Constituent Affairs. Qualified patient representatives not only have experience with a disease or condition, but are active in patient advocacy organizations, knowledgeable about treatment options, and able to grasp basic scientific principles, Klein pointed out at the recent conference on PFDD sponsored by the University of Maryland Center of Excellence in Regulatory Science & Innovation.

One FDA initiative is to develop a "roadmap" to patient-focused outcome measurement in clinical trials, reported Ashley Slagle of the Office of New Drug (OND) Study Endpoints and Labeling Development staff in the Center for Drug Evaluation and Research (CDER). The roadmap aims to establish an orderly pathway for selecting or developing instruments to accurately measure treatment benefit, she explained. Key criteria are the natural history of the disease or condition, the affected patient population, treatment alternatives, and current care standards.

— Jill Wechsler

ONCOLOGY OUTLOOK

Report Spotlights Progress, Challenges in Oncology Practice

A new study by the American Society of Clinical Oncology (ASCO) chronicles the current realities of the cancer care system and examines trends in the oncology workforce and practice environment that are affecting patient care and access. The report is titled "The State of Cancer Care in America: 2015."

According to the ASCO report, there is a wider array of treatment options than ever before for many cancers. In 2014, the FDA added 10 new treatments to its list of more than 170 approved anti-cancer agents, and also approved four new medical devices and tests that may improve patient outcomes through early detection of cancer. In addition, more than 770 cancer therapies are in the research and development pipeline and therapies are demonstrating dramatic improvements in efficacy.

However, the report noted growing challenges to high-quality care delivery, some are as follows:

- Due largely to an aging population, a dramatic 45% increase in cancer incidence is expected by 2030, leading to an overwhelming demand for cancer care and post-treatment services in the relatively near future.
- Benefits of cancer screening and treatment advances have not been experienced consistently across racial and ethnic groups, as evidenced by differences in incidence and mortality rates. African Americans, for example, are 2.5% more likely to develop cancer than whites and 19.6% more likely to die from cancer.
- Nation's ability to care for an increasing number of people with cancer depends on a workforce that is sufficient in size, diversity, and geographic reach.
- Continuation of practice consolidations, as one quarter of all community-based oncology practices report the likelihood of becoming affiliated with a hospital over the next year.
- Industry needs to find better ways to pay for and incentivize high-quality, value-based care. ASCO is currently developing and testing an alternative payment approach that reflects the current realities of oncology practices and ensures that patients receive the full range of services that are integral to their care.

ASCO made several recommendations directed to Congress, one of which calls on increasing the budgets of the National Institutes of Health and the National Cancer Institute by at least $32 billion and $5.32 billion, respectively. View the full release here: http://bit.ly/1y2htXm.

—Staff Report

CLINICAL TRIAL STRATEGY

Planning for Success in Late Phase Global Oncology Trials

Managing a successful Phase III global oncology trial presents one of the most complex challenges drug companies face within the development cycle. Phase III clinical trials require a global scope to access larger patient pools, obtain exposure to a more demographically diverse patient population, and deploy regulatory strategies that can ultimately support commercialization.

For smaller biopharma companies, where resources and pipelines are frequently limited, navigating the development and successful execution of a global Phase III trial is critical, not only to the ultimate success of the compound, but sometimes even to the survival of the company.

Given the challenges of late phase global trials, strategic and detailed planning is critical to success—especially in the first six to 12 months. The following are four study design activities every drug developer must undertake to clear cross-border barriers and deliver a successful global oncology trial.

Establish a firm scientific foundation for the trial

Prioritize study plan completion in alignment with clinical trial process. Plans that affect study start-up, such as regulatory plans, should be completed first—before tackling those which impact a trial's readout phase, such as the statistical analysis plan. All plans should address staffing, training, documentation, and compliance requirements. For example, does the plan consider global variations in imaging methods and account for differences in radiologist training? This is certainly crucial to any global oncology trial that looks at target lesions, responses, and progression as part of its major endpoints, especially in light of recent trends to leverage surrogate endpoints in lieu of overall survival for registration.

Conduct extensive and early feasibility

Performing clinical trial feasibility is one of the initial and most important steps in conducting a global clinical trial. Feasibility can help determine the best mix of countries and sites, each of which has challenges that could influence the completion of a study. Conducting extensive and early feasibility allows a better understanding of the global climate and the competition for the patient population. It can help determine where your compound fits in terms of both clinical interest and regional considerations. This includes determining provision and reimbursement requirements as well as access to marketed and available comparator or supportive drugs required by the protocol design.

> For smaller biopharma companies, navigating the development and execution of a global Phase III trial is critical, not only to the ultimate success of the compound, but sometimes even to the survival of the company.

Ensure comprehensive operational and regulatory plans are in place

Developing a model for trial start-up and enrollment timelines provides a comprehensive view from start-up to last patient that begins on day one. This

enables sponsors to allow for the "real-world" planning of a trial. Because of the variance in timelines for approvals, an understanding of the country, region, and site-specific requirements can help a sponsor navigate the concurrent processes necessary to obtain authorization for international trials. While no timeline is perfect, ones that account for delays, questions, changes, and even holidays permit realistic planning.

Engage required vendors in successful partnerships

Working with an experienced contract research organization (CRO) to develop a comprehensive set of study plans and step-by-step processes assures regional issues are proactively addressed before the first patient is even enrolled. On-the-ground knowledge, acquired via an oncology CRO's daily experience working with local regulatory agencies, local labs, logistic experts, study sites, and investigators is critical to a global oncology trial's success. Making sure your outsourcing partner has comprehensive study plans on a trial will ensure all team members, globally, understand their function and how to address unforeseen issues that may arise.

— Heather Davis, Director of Project Management, Late Phase Oncology Programs, Novella Clinical

DRUG APPROVAL PATHWAYS

FDA's Expedited Review Process: The Need for Speed

The FDA currently uses four programs to expedite reviews of drugs for serious and life-threatening diseases. Whether accelerated approval, priority review, fast track, or breakthrough therapy, each program has specific requirements and benefits, and can be used in various combinations. At the start of any drug development program, an in-depth understanding of these options is critical to ensuring the most efficient path to approval.

Accelerated approval allows the use of surrogate endpoints

In response to the AIDS crisis in the late 1980s, the FDA drafted initiatives to accelerate drug delivery and cut costs for new drugs treating serious and life-threatening illnesses and conditions, granting approval to drugs after extended Phase II trials. In 1992, in response to a push by AIDS advocates to make the investigational anti-AIDS drug azidothymidine (AZT) accessible, the FDA enacted "Subpart H" commonly referred to as accelerated approval; giving rise to expedited review of drugs by the FDA. This legislation allowed new drug applications (NDAs) to be approved based on surrogate endpoints in clinical trials including 1) markers that would be expected to confer a clinical benefit such as improved overall survival, prolonged suppression of HIV viral load in HIV, or tumor shrinkage in cancer, or 2) an intermediate clinical endpoint; a measurement of a therapeutic effect considered reasonably likely to predict clinical benefit, such as an effect on irreversible morbidity or mortality.

There is no formal application process for designating a product for development through the accelerated approval pathway. Drug sponsors that decide to pursue this pathway meet with the FDA early in drug development and agree on the following criteria:

- The unmet need that exists in the patient population being studied
- The surrogate endpoints that will be assessed
- The magnitude of benefit that must be observed using the agreed-upon surrogate endpoint
- Post-marketing commitments

Acceleration of oncology drug approval: Accelerated approval has been vital in expediting access primarily to drugs for cancer patients. From 2000 to 2012, 53% of accelerated approvals were for cancer drugs, 18% were for HIV, and 29% for "other," with cardiovascular leading the "other" category. As of July 1, 2010, 35 oncology products had obtained accelerated approval for 47 indications, and 26 were converted to full approval with an average time of conversion of 4.7 years. Following post-marketing analysis, three oncology drugs that were granted accelerated approval have been withdrawn or relabeled because of unexpected safety or apparent lack of efficacy; however, the majority of accelerated approvals have confirmed clinical benefit.

Overview of FDA's Expedited Drug Approval Programs

	FAST TRACK	ACCELERATED APPROVAL	PRIORITY REVIEW	BREAKTHROUGH THERAPY
Date established	1988	1992	1992	2012
Qualifying criteria	• Must be intended to treat serious condition • May address an unmet medical need • Supporting data can be clinical or nonclinical	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • May use surrogate endpoints to demonstrate clinical benefit	• Must treat a serious condition • Provides significant improvement in safety or effectiveness over existing therapies	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • Supporting data must be clinical
Time frame for application and FDA response	Can be requested with an investigational new drug (IND) submission or any point after applying. The FDA has 60 days to respond to request.	No formal process. Drug sponsors are encouraged to discuss the possibility with the FDA during drug development.	Requested at time of drug approval application. The FDA has 60 days to respond to request.	Can be requested with IND submission or any point after applying. The FDA has 60 days to respond to request.
Key program features	• Earlier and more frequent communication with the FDA during development • Rolling review of application • Designation may be withdrawn if drug no longer meets qualifying criteria	• Approval is granted on a conditional basis. Drug sponsor must conduct post-approval trials to confirm benefits • Application is submitted in one package • Drug is subject to expedited withdrawal	• Drug review process is shortened to six months (from the standard 10 months)	• All fast-track designation features • Intensive FDA guidance throughout development process, involving senior FDA officials • Designation may be withdrawn if drug no longer meets qualifying criteria

Source: FDA's "Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics" (June 2013)

Priority review shortens FDA review timelines

In 1992, under the Prescription Drug User Fee Act (PDUFA), the FDA agreed to improve drug review timelines, and created a two-tiered system of review times: priority review and standard review. To improve review timelines, the agency grants a priority review to applicants for drugs that 1) treat a serious condition and 2) would provide a significant improvement in the safety or efficacy for a serious condition. Priority review shortens the target period for FDA review from 10 months to six months, and this designation is often used in combination with other expedited review processes.

Fast track designation for drugs with potential to address unmet medical needs

The expedited process "fast track" was implemented under the FDA Modernization Act (FDAMA) of 1997. The designation targets drugs that are intended 1) to treat a serious condition and 2) for which data demonstrate the potential to address an unmet medical need. Fast track addresses the need to approve treatment for a broad range of serious diseases, including AIDS, Alzheimer's, cancer, epilepsy, and diabetes. An application for fast-track designation can be submitted at any time during the drug development process and can use preclinical or clinical data to show potential to address an unmet medical need. The FDA must respond to the application within 60 days. With fast-track status, sponsors benefit from the opportunity for early and frequent interactions with the FDA review team and from the "rolling review" process where portions of an application can be submitted for review prior to submitting the complete application.

Fast track of Ebola vaccines: Recently the FDA has been under pressure to fast track experimental drugs and vaccines for the Ebola virus, of which there is no known cure, following the spread of the virus in Western Africa with 8,795 reported deaths as of the end of January, according to the CDC. In October 2014, the FDA approved the use of an experimental antiviral drug which has successfully treated Ebola in lab tests. The drug has also been tested by the CDC and the NIH, though it is not expected to win approval for wide public use until late 2016. Another drug, produced by a Canadian drugmaker, has also been approved under the fast track provision and was used to treat a patient in Atlanta.

Breakthrough therapy for drugs with substantial superiority

FDASIA also introduced the breakthrough therapy designation into the FDA portfolio of expedited programs to address new trends in drug discovery and development, particularly targeted therapies (including biomarkers), often paired with companion diagnostics, for treatment of cancer, genetic diseases, and increasingly other diseases. The breakthrough therapy designation is similar to fast track and accelerated approval in that it requires the investigational drug be used for a serious or life-threatening disease. Breakthrough therapy also allows "rolling review" of drug development material being submitted to the FDA. Breakthrough therapy designation differs from the other expedited review processes by requiring the use of a clinically significant endpoint that demonstrates substantial superiority of the drug over available therapies. The breakthrough therapy designation offers more expansive benefits than the other expedited processes in that once a drug receives the tag, it is assigned an FDA committee, which meets regularly with the sponsor to devise the most efficient way to generate additional safety and efficacy data to move development forward. It is an "all hands on deck" approach, with frequent communication between the drug developer and the FDA, at the division level and across all levels of FDA management.

Between July 2012 and December 2013, the FDA received 135 breakthrough therapy requests, 41% of which were for cancer therapies.

— Shahza Somerville, Medical Writer and Clinical Research Specialist at Technical Resources International (TRI), and Jessica Holden Kloda, Associate Director of Regulatory Affairs at TRI

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Giving Pharma Credit for Medical Innovation

Study shows that industry contributions to R&D go well beyond the applied area of clinical testing

In late January 2015, Senator Elizabeth Warren (D-Mass) submitted a new bill to Congress called the Medical Innovation Act. The bill would require major pharmaceutical companies that are convicted of breaking the law to pay 1% of their annual profits for each drug they develop that can be traced to government-funded research. Warren estimates that the bill—if passed—would eventually deliver an estimated $6 billion each year in incremental support for the National Institutes of Health (NIH).

Among the public and private sectors within the research community, this bill—more affectionately known as the "swear jar" bill—has stimulated debate about who should receive credit for medical innovation and whether additional investment in NIH-based research will have its intended impact. The bill has also stirred up the perennial and deep-seated misconception that drug discoveries come primarily from government-based research activity and that industry lurks about waiting to profit handsomely from discoveries paid for by public tax dollars.

A new study by the Tufts Center for the Study of Drug Development (Tufts CSDD) informs this debate and characterizes the highly interdependent relationship between public and private sectors that drives medical innovation. The results show that drug discovery through clinical development is supported by a complex community of contributors, including industry-academic partnerships, venture capital, disease foundations, public-private, and private-private pre-competitive consortia.

The public sector is the dominant contributor in basic research. But industry is the dominant contributor in discovery, manufacturing, lab and animal model testing, and in drug development.

The Tufts CSDD team also examined how much funding would be required from the NIH and other government sources to replace private sector contributions to new drug research and development. The team concluded that, conservatively, the NIH budget would have to increase by approximately two-and-half times to maintain the current volume of new treatments in development.

Methodology

The Tufts CSDD team analyzed 26 therapies deemed the most important and transformative drugs in healthcare over the past 25 years based on a survey of nearly 200 expert physicians from the top 30 U.S. academic medical centers. Tufts CSDD compiled in-depth case studies on these individual therapies; analyzed data from proprietary and commercial databases; conducted online searches; and reviewed published literature from professional journals, the trade press, textbooks, and historical reviews of drug origins. The study scope was expansive, requiring an assessment of global R&D activity spread out over an average of 25 years from discovery to approval.

Kenneth A. Getz
MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCRP, both in Boston, MA, e-mail: kenneth.getz@tufts.edu

Contributions to various drug development milestones were mapped for each therapy including: disease process, drug target, mechanism of action, drug concept, isolation and purification, synthesis and early testing, patenting, lead optimization, preclinical studies, formulation and manufacturing protocols, clinical development, approval, and launch. Contribution assessment was then organized around four largely sequential R&D domains or categories—basic research, discovery, chemistry/manufacturing & formulation/controls (CMC), and development. Multiple team members conducted independent reviews of the contribution assessments to reach a consensus assessment.

For the economic analysis, the Tufts CSDD team used a methodology it has developed, validated, and applied for decades to determine the total out-of-pocket R&D costs to develop each therapy. NIH budget figures were gathered from publicly available sources.

Credit where credit due

The results indicate that the private sector is the dominant contributor in three out of the four primary R&D domains. And of the 26 major therapies evaluated, only four (15%) appear to have been almost completely researched and developed by the private or public sector alone. All others involved a high level of collaboration and shared contribution.

The table on page 22 indicates the contribution of the public and private sectors across the four R&D domains.

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R&D Support by Sector

CONTRIBUTION BY	BASIC	DISCOVERY	CMC	DEVELOPMENT
Public sector	54%	15%	0%	4%
Private sector	27%	58%	81%	73%
Jointly	19%	27%	19%	23%

Source: Tufts CSDD

Table 1. A comparison of contributions across the four domains of pharmaceutical research and development.

The public sector dominated the basic science domain. More than half (54%) of the basic science milestones were achieved largely by the public sector. More than one-quarter (27%) of the basic science milestones were achieved by the private sector. Contribution to the basic science milestones by one sector over another was indiscernible for nearly one-out-of-five therapies.

In the discovery domain, the private sector was the dominant contributor. The private sector made the dominant contribution to achieving discovery milestones for 58% of the therapies. Approximately one-out-of-seven (15%) of the discovery milestones was achieved by the public sector.

The private sector also made the dominant contribution to achieving CMC and drug development milestones. The private sector was the dominant CMC contributor on the vast majority of therapies (81%). Approximately 20% had no discernible dominant contribution. And the private sector was the dominant contributor to achieving development milestones for 73% of the innovative therapies. This compares with the public sector serving as the dominant contributor in the development phase on 4% of the therapies.

With respect to the economic analysis, the Tufts CSDD team determined that the total aggregate out-of-pocket cost for the most innovative drugs developed between 1987 and 2002 was $128 billion (in year 2013 dollars). On an average annualized basis, this amounts to about $8 billion in aggregate costs. R&D activity typically continues long after a drug has received approval to support testing of new dosage levels, new formulations, new indications, and to meet regulatory post-marketing commitments. Tufts CSDD determined that an additional $41 billion was spent on the most innovative therapies for post-approval R&D activity. The total aggregate lifecycle R&D costs for the most innovative therapies came to $169 billion or an average annual aggregate cost of $10.6 billion per year.

> **Open innovation platforms supported by the public and private sectors are essential under the new R&D paradigm.**

Based on its annual expenditures, the NIH would have to have nearly doubled its budget to replace industry contribution to develop the most innovative therapies. These estimates are very conservative. The level of NIH support required to replace industry contribution would no doubt be substantially higher; the estimates are based on the cost to develop therapies during the 1987 to 2002 period. These costs have increased dramatically due to many factors, including increased scientific and operating complexity associated with more demanding disease conditions and regulatory requirements. In addition, the NIH's relative inexperience in managing later stage R&D activity would likely drive R&D costs higher than those borne by industry.

Conducive to collaboration

The commonly held belief that the private sector adds limited value but reaps huge profit on the hard work and tax-supported backs of the public sector research community is simply a myth. Far from being exploitive bystanders, pharmaceutical, biotechnology, and medical device companies make substantial contributions.

The Tufts CSDD study demonstrates that industry contributions go well beyond the applied area of clinical testing; the private sector plays an integral and essential role in translating knowledge about biological processes into a medicine or vaccine providing clinically meaningful benefit at minimal risk. The replacement of private sector contribution by the public sector is completely unrealistic. Even more compelling, the absence of private sector contribution to medical research would render the return on taxpayer investment in the basic sciences largely inconsequential.

Public-sector funding for medical research continues to face significant constraints. Pressures from patient communities and the healthcare environment are growing. As a result, demand for private sector contribution and collaboration with academia and government will continue to intensify.

Open innovation platforms supported by the public and private sectors are essential under the new R&D paradigm defined by patient community engagement. These platforms will be the most effective when medical research stakeholders are best informed about, and acknowledge, the contributions that each sector—and each collaborative partner—brings to advancing public health.

To review a detailed report on the Tufts CSDD *study, go to: http://csdd.tufts.edu/files/uploads/PubPrivPaper2015.pdf.*

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Overcoming Challenges in Hematological Cancer Trials

Andrew Zupnick, PhD

Successful conduct of hematological malignancy trials requires addressing several unique complexities.

Conducting successful clinical trials in hematological malignancies requires an understanding of a rapidly evolving treatment paradigm that is increasingly nuanced, complex, and patient-directed. Just as the underlying differences in biology and prevalence between blood cancers and solid tumors necessitates differences in treating patients, so, too, do they demand differences in clinical trial expertise and conduct. Sponsors developing hematological oncology therapies must capitalize on the principles and infrastructures shared by solid tumor oncology trials while adapting endpoints, study designs and considering patients' experiences to address the particular challenges related to investigating candidate treatments for blood-based cancers. This article examines the nuances of effectively and successfully conducting hematological oncology clinical trials.

Blood cancer basics

In the United States, someone is diagnosed with a blood cancer every four minutes, and every 10 minutes, these malignancies result in a death.[1] Despite this incidence, the three most common forms of blood-based cancers—leukemia, lymphoma, and myeloma—comprised only an estimated 9% of all new cancers and 9% of all cancer deaths in 2013 in the U.S.[2] In comparison, the three most common U.S. solid tumor cancers—breast, lung, and colon cancer—together accounted for an estimated 34% of new cancer patients and 43% of cancer deaths in 2013.[2] (See Figure 1 on page 26). Globally, leukemia, multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma collectively accounted for only 6.5% of all cancer patients in 2012, excluding non-melanoma skin cancer.[3]

Despite a smaller incidence within the total oncology patient population, the global market for hematological cancer drugs reached an estimated $18.7 billion in 2012, with a projected target of at least $28.8 billion by 2017, equating to a compound annual growth rate of 9%.[4]

The growing hematological oncology therapy market will be fueled by the success of some of the more than 3,000 medicines in development for cancers.[5] Driven in part by the application of new scientific knowledge and technologies to isolate and study the biology of malignant cells, a significant portion of hematological cancer medicines can truly be called novel. Of the 818 hematological oncology investigational projects underway, 627 had the potential to be first-in-class medicines, according to a January 2013 assessment.[6]

The ongoing research investment in understanding the fundamental biology of hematological malignancies will produce an enhanced and refined understanding of cancer pathologies in general as well as increasing the number of targeted therapies for blood cancers and enabling truly personalized treatments. Therefore, sponsors that ensure careful design and precise execution of their hematological oncology clinical trials will yield data that can inform, and perhaps significantly impact the greater oncology community.

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Key Learning Objectives:

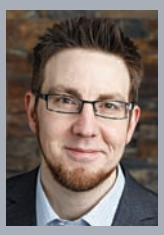
- Review the standards and regulations in place
- Understand the risks and mitigate them
- Learn what de-identification is and isn't–then how to apply it to clinical trial data

WHO SHOULD ATTEND

- C-Level (CMIO, CIO, CPO,CEO, COO, CFO)
- Privacy Officers
- Pharma
- Compliance
- Medical Researchers
- Analysts

PRESENTERS

KHALED EL EMAM
CEO
Privacy Analytics, Inc



LUK ARBUCKLE
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PRIVACYANALYTICS
Data Anonymization Solutions

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APPLIED CLINICAL TRIALS
Your Peer-Reviewed Guide to Global Clinical Trials Management

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Statistical Comparison

Common Types of Cancer *(United States, 2013)*	% of New Patients Diagnosed Annually	% of Cancer Related Deaths
Blood-Based Cancers Leukemia, Lymphoma, Myeloma	9%	9%
Solid Tumor Cancers Breast, Lung, Colon	34%	43%

Source: Zupnick

Figure 1. Blood-based cancers comprised only an estimated 9% of all new cancer cases and 9% of all cancer deaths in 2013 in the U.S.

As an example, several years ago, Novella Clinical was approached by a biotech company to help rescue a pair of pivotal Phase III trials for its CXCR4 antagonist in development for hematopoietic stem cell transplantation. The sites participating in the trial had nearly shut down, refusing to submit any further patient data due to the supporting contract research organization (CRO) overwhelming them with nonsensical queries. Simply put, the data and clinical management teams did not understand that, fundamentally, these patients are incredibly sick, and an "abnormal" lab value can be "normal" in this setting. For example, one would expect neutropenia or thrombocytopenia to occur following a transplant, and should not necessarily query lab data showing out of "normal" range white blood cell or platelet counts.

Novella was brought in to leverage its hematological oncology expertise in data management and biostatistics to rebuild the clinical database, clean up a substantial amount of the queries and help perform the analysis to support a new drug application (NDA). Ultimately, Novella turned the trial around and Mozobil® (plerixafor) for stem cell mobilization in NHL and MM patients was approved.

Steps to high performance HemOnc trials

A hematological oncology trial is fundamentally different than a solid tumor study. Patient access alone is more difficult, as evidenced by the incidence rates previously mentioned. Researchers should evaluate a hematological oncology study design relative to the feasibility of successfully enrolling and executing the trial and, if deficient, be able to offer modifications or alternative approaches that will lead to successful enrollment. To do so, they first need to understand the pathology, clinical manifestations, and current treatment guidelines of the specific hematological cancer under study to fully comprehend all aspects of the most appropriate trial design. Sponsors and their partners must consider how these cancers influence the selection and precise use of terminology in defining important study parameters, of appropriate trial endpoints, and of data management technologies, as well as the selection and experience of patients.

Defining the disease. The correct clinical research use of terminology associated with hematological cancers requires familiarity and understanding. This defining process can present a notable learning curve for sponsors, trial staff, or partners.

For example, if a tumor forms in the lung, it is considered lung cancer, which has various subtypes, and if it spreads to other parts of the body, it is still called metastatic lung cancer. In contrast, bone marrow can be the starting location for several distinct cancers, many of which have their own subtypes and some of which can change and develop with time into a new cancer.

Other classification systems define leukemia by the speed at which it develops, either chronic (slow) or acute (more quickly), as well as by the type of white blood cell affected, usually lymphoid or myeloid cells. Similarly, NHL is comprised of a large group of lymphocytic cancers divided into aggressive (fast-growing) and indolent (slow-growing) types that occur from either B-cells or T-cells. Classifying NHL is challenging not only because there are many subtypes, but also because of the methods used to determine the subtype. The World Health Organization (WHO) devised a system that not only uses cell morphology but also includes assessments of cell genetics and surface protein receptors.[7]

Recently, the most significant advance to clinical trial design, and an early glimmer into the potential of personalized medicine, is the need to identify patients with specific biomarkers before the patient can be considered eligible for study participation. Depending on the frequency of the marker used as entrance criteria, or even whether the marker is tested as standard of care at a given institution, the population of potential patients may be significantly reduced and necessitate a consequently large increase in screenings of patients. For example, adding the criteria that acute myeloid leukemia (AML) cancer patients be positive for a FLT3-internal tandem duplication (ITD) mutation reduces the patient population to just 25% of all de novo (first line) AML patients.[8]

Understanding the treatment landscape. A sponsor must be knowledgeable of the bigger picture presented by the competitive hematological oncology treatment landscape, including current treatment guidelines and clinical practices. To appropriately drive development strategy in

Breast, Lung, and Lymphoma Trials: A Comparison[13]

TRIALS (%)	BREAST	LUNG	LYMPHOMA
Purpose of intervention	(n=1030)	(n=809)	(n=584)
Treatment	72.3	86.9	95.5
Prevention	6.7	2.5	1.2
Diagnostic	8.5	6.1	2.1
Supportive care	9.6	2.3	1.0
Intervention	(n=1067)	(n=824)	(n=590)
Drug	64.5	76.1	85.3
Procedure	19.0	12.4	10.8
Biologic	8.0	9.1	22.4
Behavior	7.0	1.2	0.2
Device	4.0	1.9	0.3
Radiation	8.2	13.2	6.3
Genetic	3.0	3.2	5.3
Other	17.9	12.3	12.9
Completion status	(n=1067)	(n=824)	(n=590)
Recruiting	61.3	60.8	62.2
Enrolling by invitation	1.6	1.1	0.7
Active, not recruiting	14.8	15.7	13.4
Completed	10.2	8.5	9.2
Suspended	0.5	1.3	1.0
Terminated	2.5	2.8	3.6
Phase—%	(n=669)	(n=679)	(n=529)
0	0	0.1	0.6
1	11.1	15.2	18.0
1/2	12.1	10.9	14.6
2	52.8	56.0	55.0
2/3,	1.1	0.9	1.3
3	18.4	13.8	8.9
4	4.2	3.1	1.7
Interventional model—%	(n=602)	(n=595)	(n=464)
Single-group	56.3	58.3	77.8
Parallel	40.9	39.5	21.8
Crossover	1.5	1.2	0.2
Factorial	1.3	1.0	0.2
Masking—%	(n=706)	(n=664)	(n=525)
Open	87.1	88.4	98.1
Single-blind	2.1	0.9	0.4
Double-blind	10.8	10.7	1.5
Treatment allocation—%	(n=675)	(n=641)	(n=488)
Randomized	46.1	42.9	19.3
Non-randomized	53.9	57.1	80.7
No of arms—%	(n=701)	(n=677)	(n=531)
1	55.9	55.1	76.1
2	34.5	36.2	18.3
3	6.3	5.6	2.6
≥4	3.3	3.1	3.0
Enrollment—no.			
Mean	280	163	82
Median	70	60	45
Location—%	(n=682)	(n=661)	(n=509)
North America only	49.7	43.0	57.4
Outside North America only	41.8	46.1	35.0
Both locations	8.5	10.9	7.7
Institutional mix—%	(n=682)	(n=661)	(n=509)
Single institution	49.9	52.5	47.3
Multicenter	50.1	47.5	52.7
Mean no. of facilities	16	19	10
Median no. of facilities	1	2	1
Funding	(n=745)	(n=703)	(n=558)
Industry	50.2	45.5	44.6
NIH/NCI	12.5	13.4	8.0
Other	37.3	41.0	47.5

Source: Zupnick

Table 1. A patient-screening comparison.

hematological oncology, a sponsor also must understand how to assess an investigational treatment's effect on the underlying disease, not just the patient's symptoms, so as to discern efficacy and safety comparative to current practices. Such evaluations will involve complex assessments using intricate endpoints that may involve counts of white blood cells, neutrophils, myeloblasts, myelocytes, as well as bone marrow measures, the spleen and the liver, among others.

In addition, understanding the investigational therapy is critical. As more and more therapies have the potential to be first-in-class, such as antibody-drug conjugates or mutationally-selective inhibitors, potential clinical trial sites will likely have little to no experience with these new treatments. This knowledge gap can be addressed with appropriate site staff training before and during the trial. Study-specific training often is not just about the therapy but also the processing of complex and sensitive lab samples and the use and measurement of specific targeted endpoints, such as biomarkers.

Determining endpoints. The determination of endpoints differs significantly between solid tumor and hematological oncology. Most solid tumor cancer trials rely on the Response Evaluation Criteria in Solid Tumors (RECIST) to define a participant's improvement/response, worsening/progression or stability. In contrast, the very nature of blood-based cancers

requires that treatment trials rely on different measurements to determine treatment-related changes and disease progression, which can add more complexity to trial design, conduct and assessment.

Overall survival (OS) remains the gold standard when evaluating cancer treatment effectiveness. However, progression-free survival (PFS) is the most commonly used surrogate endpoint for trials involving advanced cancers.[9] Other progression-related OS surrogate endpoints include disease-free or event-free survival, response rate or objective response rate and time to progression.[9]

The smaller, single-arm design used in many hematological oncology trials usually precludes using time-to-event endpoints to reliably interpret treatment effects[10] and determine OS. Therefore, these trials measure event-free survival, remission rates, duration of response, as well as laboratory measures of biological activity. Major molecular response endpoints also are not uncommon in hematological oncology trials but require great specificity in determining what to measure and the techniques involved, based on the disease under study and whether it is acute or chronic. In the care setting of patients with chronic myeloid leukemia (CML), for example, a polymerase chain reaction (PCR) assay can evaluate molecular responses, namely measures of transcription levels of a specific fusion protein. Such molecular measures are now being adapted to the research setting. For example, entry criteria in CML trials using treatment-free remission as an endpoint require that patients achieve deep, molecular response levels.[11]

Hematological oncology trials also take advantage of technological developments to measure survival, particularly imaging, to provide greater specificity. For example, the 2011 biologics license application (BLA) submitted to the FDA for brentuximab vedotin was the first to use the agency's response criteria for lymphoma drugs, set forth in 2007,[10] which included FDG-PET (18F-fluorodeoxyglucose positron emission tomography) scans in the response assessments. The FDA considered PFS acceptable as an endpoint to confirm clinical benefit because an OS endpoint would not likely occur within a reasonable time frame. The BLA used data from two single-arm studies, both designed to show superiority using PFS as a primary endpoint and OS as a secondary endpoint. The FDA used these data to grant accelerated approval of the biologic for patients with Hodgkin's lymphoma after failure of autologous stem cell transplantation (ASCT) or of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and for patients with relapsed systemic anaplastic large-cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.[10]

As companies create a development strategy for a compound, the choice of endpoints is very important. Often, sponsors need to strike a balance between FDA-supported endpoints, cost, time, and other endpoints, markers or measures that can quantify or qualify an efficacy signal but may not meet regulatory stringency. Designing trials accurately, understanding appropriate endpoints and measuring response using the correct technology are keys to trial success.

Resourcing study management. Whether in-house or through a partner, clinical research associates (CRAs) need to understand the significance and implications of blood count shifts as well as of transfusions and dosing timing. In the seriously ill patient populations of most hematological oncology trials, certain blood counts are expected to fluctuate because of their disease. For example, anemia in these patients can affect both drug activity and toxicities, so monitoring the anemia and its treatment in trials is important. When hemoglobin counts drop below a certain level, patients require a blood transfusion, which will raise the hemoglobin count. However, the hemoglobin count may also rise after a patient receives a treatment dose. An experienced CRA will know if such fluctuations are prompted by the transfusion, the dosage or the disease state.

Selecting trial sites. Many pharmaceutical and biotechnology companies are pursuing compounds that target hematological malignancies, and combined with an inherently rare patient pool, this naturally causes competition for investigator and institution participation, patient enrollment and key opinion leader relationships. Moreover, the world of hematological oncology specialists is even smaller than that of solid tumor specialists, making competition that much more intense. For a global trial, the rarity of some hematological oncology diseases can result in a lack of knowledgeable investigators or inconsistencies in standards of care from region to region. These variations can limit regional or country-specific options in site selection, which can have implications for trial conduct and regulatory clearance plans.

While the 2012 ASCO National Census of Oncology Practices found more than 70% of all responding practices reported offering a hematological oncology specialty for patients, only 26% of all practice types participated in clinical trials.[10] A mere 11.3% of responding practices defined themselves as academic, with either teaching or research activities,[12] making it clear that highly knowledgeable and experienced oncologists and hematologists practicing in community settings represent a significant source of referrals for clinical trials. However, at smaller community-based sites, a sponsor may need to offer more significant trial management support.

Consider patients' experiences. Sponsors of hematological oncology studies need to take several patient needs into consideration when recruiting, enrolling, and retaining patients. The trial's educational materials must not only clearly transmit information about potential treatment benefits and risks regarding their disease but also must include the potential impact study participation may have on one's quality of life, such as the number of clinic visits, blood draws, and radiographic studies as common in lymphoma.

Additionally, trial teams must be aware that patients with hematologic cancers have disparate potential viewpoints that set them apart from solid tumor patients and that might impact enrollment and retention strategies. Some patients with lymphoma or leukemia, for example, have a chronic clinical course that extends for years, even decades. These patients are frequently interested in the potential a trial can offer, but want the confidence that an investigative therapy is likely effective and will not interfere with their lifestyle. They usually are less concerned about the pace of a trial and more concerned about invasive procedures, such as repeat biopsies or bone marrow exams, because of their risks.

The opposite is true for patients with acute hematological cancers such as acute leukemia. Time is highly important to them, and they seek immediately available clinical trials and "instant" therapies they perceive as offering the potential for life extension, even if trials involve more invasive interventions, multiple clinical visits, or radiographic studies. These patients find trials requiring long evaluations and limited chances to participate unappealing, but readily accept coming to the clinic frequently to confirm an investigative therapy is working.

The better a hematological oncology trial can address the treatment agendas of individual patients, the more success the study will have in recruitment and completion.

Conclusion

General patient rarity (most of these indications can be classified as orphan) combined with limited treatment specialists and centers, an intense competing trial landscape, and the potential for shifting standards of care both over time and across global regions makes proper site selection that much more critical to a study's success right out of the gate. Disease terminology, classification, and trial endpoints/response assessments are highly complex and can even morph over time, highlighting the need for an active knowledge base in this space when designing the trial and when assigning the study team. Finally, the differences between the potential speed of progression within an indication (e.g., acute vs. chronic leukemia) and the resulting impact of invasive or frequent procedures on a patient's willingness to participate in a given trial should be taken into account when designing the protocol.

Ultimately, the future looks bright for hematological oncology treatment with so many novel drugs and personalized approaches in development; a thorough understanding of the potential challenges in implementing clinical trials in this complex space will help speed the process to bring new therapies to patients in need.

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Improving Oncology Trials Through Adaptive Designs

Dirk Reitsma, MD, Austin Combest, Jürgen Hummel, Ashley Simmons

How the practical application of these methods can help overcome the complex demands of cancer trials.

Today's rich oncology pipeline—accounting for nearly 25% of agents in clinical development—promises much needed advances in cancer therapy.[1] That promise dims in the face of other discouraging statistics: only 7% of oncology agents entering Phase I clinical trials gain marketing approval[2] while only 34% of Phase III oncology trials achieved statistical significance in primary endpoints.[3]

The cost, time, and numbers of patients required to conduct conventional oncology clinical trials continue to escalate. The complex demands of evaluating new targeted therapies add to this burden. Novel methodologies are available that make trials more efficient and informative so that precious resources of patients, time, and money are invested in studies with the greatest chances of success.

Adaptive trial design offers opportunities for improvement by shortening the time needed to answer key research questions, reducing the number of patients needed for evaluation, and improving the quality of decision-making to increase overall success rates. The use of adaptive designs also raised scientific and regulatory questions that slowed adoption by the biopharmaceutical industry. A growing body of experience culminated in the U.S. Food and Drug Administration's (FDA) 2010 draft guidance, "Adaptive Design Clinical Trials for Drugs and Biologics," which details adaptive approaches and encourages their use.[4]

FDA defines an adaptive study as one that "includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study." Five adaptive designs—including blinded sample size re-estimation and halting early for lack of utility—are cited as "well-understood." FDA encourages drug developers to use these approaches for all studies. Seven "less well-understood" designs—including unblinded applications that use interim estimates of treatment effect for endpoint selection and sample size re-estimation—should be reserved for exploratory studies while more experience is gained.

This regulatory underpinning supports wide application of adaptive design in oncology drug development. Its positive impact can be seen in the groundbreaking breast cancer trial I-SPY 2 ("Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis"), which uses adaptive design to streamline identification of active drugs and predictive biomarkers.[5] I-SPY 2 suggests a model for new, adaptive design-based approaches to advance the oncology drug-development process.

Traditional Design: Poor information leads to poor performance

Traditional designs contribute to high failure rates and escalating costs because answers to pivotal research questions are obtained only at the end of the trial. Trials using fixed designs rely on assumptions that may be found to be incorrect at the end of the study. Faulty assumptions used in

Key Performance Metrics

Average Cost per Patient: Oncology vs. All Rx categories (2011)[6]
Phase II: $73,000 (vs. $36,000)
Phase IIIa: $57,000 (vs $47,500)
Phase IIIb: $66,000 (vs $47,000)

Overall Success Rates (1993-2004)[2]
7.1% of Phase I oncology entries were approved
19.0% of Phase I entries in all Rx categories were approved

Phase III Success Rates (2003-2010)[3]
34.0% of trials achieved statistical significance in primary endpoints

Source: Reitsma et al.
Table 1. Performance measures in oncology trials.

Common Adaptations

- Stopping early (or late, i.e., extending accrual) with a conclusion of superiority or futility
- Adaptively assigning doses to more efficiently assess the dose-outcome relationship
- Adding or dropping arms or doses
- Seamless phases of drug development within a single trial
- Changing the proportion of patients randomized to each arm
- Adaptively identifying in on an indication or responder population
- Changing accrual rate

Source: *Berry D., Nat Rev Clin Oncol 2012; 9: 199-207*
Table 2. Eight common types of adaptations.

underpowered Phase I and Phase II trials yield poor information on which to base decisions about Phase III designs where the impact of failure is greatest due to the large number of patients and time involved. The cumulative effects of the traditional approach are low overall success rates and high costs (See Table 1).

Advancing oncology drug evaluation depends on: 1) selecting the best drug candidates; 2) identifying and eliminating failures as early as possible; and 3) designing trials to identify the right dose, for the right disease, in the right patients as early as possible. With thousands of potential drugs awaiting development—and with relatively few of these likely to demonstrate efficacy—earlier information and better-focused evaluation are critical to improving success rates. Adaptive trial designs are especially well suited to this purpose.

Incremental decision-making improves research outcomes

Adaptive designs leverage accumulating data to modify trials as they progress, making better decisions at each sequential step. Adaptive approaches use early findings to improve the next phase in a flexible process that can accelerate timelines, reduce costs, and generate the most knowledge from the smallest number of patients.

Traditional designs use a probabilistic statistical approach. Decisions regarding dosage, randomization, and sample size are made in advance and usually do not change throughout the trial. Instead of making pivotal decisions with limited information before a trial, adaptive designs use accruing information to obtain relevant data that inform and improve critical decisions. Data are analyzed continuously or at designated interim points, and results are used to shape future design parameters such as doses, disease indications, or populations being studied. Using this flexible approach, the trial becomes a learning tool that applies evolving knowledge to drive subsequent decisions.

> **Traditional designs contribute to high failure rates because answers to pivotal research questions are obtained only at the end of the trial.**

Roles of Bayesian statistics, simulation, and biomarkers

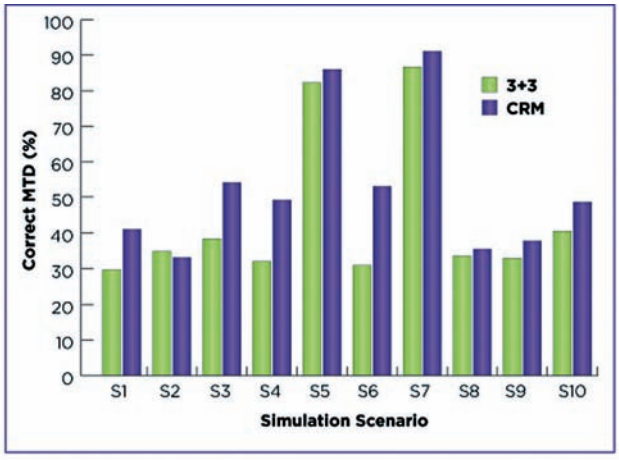
Adaptive designs can incorporate more than one adaptation in a trial and may address a number of research questions simultaneously. A single trial can be designed to evaluate multiple dose regimens, indications, drug combinations, and even multiple drugs.

For example, a seamless Phase II-III breast cancer trial might include adaptive approaches to stop early for futility, assess dose response, drop or add arms, change the proportion of patients randomized to each arm, and enrich the patient population with subjects most likely to respond. Table 2 lists eight adaptive settings commonly used in drug development and particularly relevant for oncology trials.[6]

Bayesian statistics in adaptive design. Adaptive designs often use Bayesian statistical methodology to model complex scenarios. In Bayesian approaches, statistical models require the formulation of a set of prior distributions for any unknown parameters, in addition to the parts of the model based on the traditional probability distribution of observations. Multiple sources of information are combined to make inferences, allowing researchers to test assumptions based on both direct observations and additional information on neighboring doses, different populations, similar compounds, preclinical modeling, genetic targeting, and historical data. Repeated analyses can be conducted within a study—and even across studies—using sequential analysis techniques. Results can be used to inform the design of the current trial.

Simulation informs optimal design. While fixed designs depend on theoretical justification of trial behavior, adaptive designs are more complex and depend heavily on simulations to understand trial behavior, efficiencies, and risks as inputs

Correct Selection of Maximum Tolerated Dose



Source: *Parke T., Tesselia Technology Consulting, 2010*

Figure 1. Comparing the CRM and 3+3 methods in identifying the maximum tolerated dose (MTD).

to inform and optimize trial design. Depending on the phase and design, regulators may require submission of simulation results to justify the scientific credibility of an adaptive trial[4], particularly if the data is intended to support a regulatory approval. Specialized simulation software, such as FACTS, is available to assess key performance characteristics including power, Type I error, bias, and average sample size.[7]

Biomarkers provide early information. Biomarkers are important in adaptive designs to provide early measures of efficacy. Since early data may be used to modify a trial as it progresses, the traditional long-term oncology endpoints of survival and progression-free survival are of less benefit. To satisfy this purpose, biomarkers do not need to be validated surrogates. Berry notes that early findings based on "auxiliary markers [that] might be correlated with, and predictive for, the primary endpoint … may be incorporated into the trial design to help guide the adaptive aspect of the design."[7] Useful markers might include early clinical outcomes (such as imaging, response, and progression), serum markers, or molecular markers from tumors via biopsies. In a provocative article, Verweij suggests that functional target pharmacology studies followed by proof-of-concept studies could replace traditional Phase I, II, and III trials, given that early tumor shrinkage—as measured by Response Evaluation Criteria in Solid Tumors—still appears to be the most reliable biomarker.[8]

Improves Phase I dose determination

The primary goal in Phase I is to determine maximum tolerated dose (MTD) for the experimental agent. Over- and under-estimation of the true MTD is a common problem in oncology trials, most of which identify MTD using the "3+3" method. An emerging adaptive approach, called the Continual Reassessment Method (CRM), yields more precise MTD determination and increases the likelihood that the true MTD is used in Phase II.

Traditional 3+3 method. In the 3+3 method, dose escalation steps are defined prior to the trial. A cohort of three subjects receives the drug at a starting dose based on preclinical data. If no toxicity is observed, another cohort of three subjects is added and the dose is escalated to the next level. If one of three subjects experiences dose-limiting toxicity, another three-patient cohort is added at the same dose, and dose escalation continues. If any additional toxicity is observed, the lower dose is declared to be the MTD.

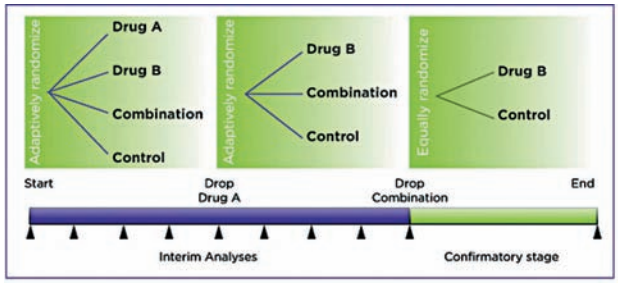
A 1999 analysis reported that when using the 3+3 method, "the probability of recommending the (correct) MTD at the end of the trial … never exceeds 44% and is most often closer to 30%."[9] Poor MTD identification is attributable to the tendency to select larger incremental "jumps" in order to observe toxicity more quickly in fewer steps. The true MTD often resides in a smaller incremental dose and is not observed.

Adaptive CRM design. The Continual Reassessment Method pinpoints the true MTD more precisely by efficiently evaluating more dose levels. CRM models the probability of the MTD as a function of dose at each dosage level and continuously refines it. The 3+3 method bases the next dose allocation (and, therefore, the level that will eventually be declared the MTD) on the last cohort of subjects, while ignoring the data from the previous cohorts. CRM uses all the data to update the estimation of the MTD and to allocate the next patients, either in cohorts or continuously. The model is frequently updated and improves with accruing data.

In the majority of cases, CRM yields better estimation of the MTD and can allow for more rapid progression through early dosing levels depending on the operating characteristics and rules that are established in the design. Although the CRM approach is more complex and requires high levels of modeling and simulation, experience has proved its value in identifying true MTD with a higher level of confidence. As shown in Figure 1 adapted from Parke, CRM is better than 3+3 at identifying the correct dose level in nine of the 10 scenarios presented. In Scenarios 1, 3, 4, and 6, CRM was substantially better, providing a 10% higher probability of identifying the MTD than the 3+3 method. In Scenario 2, the CRM and 3+3 approaches yielded very similar results.[10]

Additional CRM benefits. Parke cites additional advantages of CRM: "Unlike the 3+3, its operating characteristics can be easily optimized in light of the current circumstances, different levels of toxicity can be targeted, different cohort sizes used and different levels of accuracy required before stopping, offering better determination of the MTD at the

Seamless Phase II-III Trial



Source: The National Academy of Sciences

Figure 2. A seamless Phase II-III trial to evaluate two drugs alone and in combination.

cost of greater sample size."[10] Seamless Phase I-II trials can be designed to allocate subjects based on continuing information on both tolerability and efficacy, an approach that shortens timelines. Another benefit is that patients involved in dose determination may continue to participate in activity evaluation—an important advantage from an ethical point of view.

Slow adoption of CRM. Despite current literature demonstrating the superiority of CRM in determining the MTD, most Phase I and Phase I-II oncology trials continue to use the 3+3 method, likely based on sponsor and investigator level of familiarity. Our search using the keywords "adaptive," "Bayesian," "CRM," "3+3," and "escalation" found a total of 12 Phase I and Phase I-II dose-escalation trials published in *The Oncologist* (four trials) and the *Journal of Clinical Oncology* (eight trials) from August 2012 through August 2013. All 12 trials used the 3+3 design, confirming the 2013 review by Ji and coworkers, which reported "... more than 95% of Phase I studies have been based on the 3+3 design."[10]

Adaptive approaches in Phase II improve Phase III trials

Improving dose-response evaluation. Adaptive designs can be used to efficiently evaluate several active doses in Phase II without necessarily increasing the sample size. Evaluation of more active doses provides a better understanding of the dose-response relationship, reducing the likelihood of failures due to suboptimal dose selection in Phase III. Ineffective or unsafe dose levels can be discontinued early, and the majority of patients can be allocated to the dose levels most likely to be active.

Improving identification of target populations. Increasing genomic knowledge of cancer subtypes is driving the need for efficient drug evaluation in targeted patient populations.

Bayesian Predictive Probability of Success for Veliparib

SIGNATURE	PROBABILITY VELIPARIB IS SUPERIOR	PREDICTIVE PROBABILITY OF SUCCESS IN 300-PATIENT PHASE III TRIAL
All HER2-	92%	55%
HER2-/HR+	28%	9%
HER2-/HR-	99%	92%

Source: Reitsma et al.

Table 3. The graduating arm is triple-negative (HER2-/HR-) subset with a 93% Bayesian probability of success in a 300-patient Phase III trial.

The milestone genetics study of breast tumors published in 2012, for example, identified four distinct subtypes of breast cancer, suggesting targets for new drugs and better uses of existing drugs.[11] As noted by Esserman and Woodcock, "The inability (or lack of explicit effort) to identify and incorporate specific disease subtypes into trial design inhibits the development of more cost-effective drugs that target specific populations," a dilemma that demands new clinical trial designs that can address disease heterogeneity and complexity.[5]

> **Increasing genomic knowledge of cancer subtypes is driving the need for efficient drug evaluation in targeted patient populations.**

Adaptive Phase II designs can be instrumental in identifying the appropriate patient population for Phase III evaluation. Identification of the right subpopulation can have a dramatic impact on the number of patients required in Phase III trials to demonstrate efficacy. For example, suppose one-half of subjects with non-Hodgkin lymphoma respond well to a drug, as measured by a 60% hazard ratio; the other half benefit by only 10%. To show superiority in a Phase III trial with all patients enrolled at 90% power, 530 events would be required. But in a trial with the subpopulation of more positive responders, only 210 events would be needed.

Halting for futility. Preplanned futility analysis based on interim data can be used to stop a study that is unlikely to meet its primary endpoint. Interim futility analysis also can allow developers to continue a study with greater confidence of success in Phase III. For example, a simple preplanned futility analysis was conducted in a Phase III multicenter study comparing a new therapy to standard of care in patients with progressive and/or recurrent nonresectable glioblastoma multiforme. The target sample size was 323 randomized patients. Recruitment was difficult;

Bayesian Predictive Probability of Success for Neratinib

SIGNATURE	PROBABILITY NERATINIB IS SUPERIOR	PREDICTIVE PROBABILITY OF SUCCESS IN 300-PATIENT PHASE III TRIAL
ALL	92%	44%
HR+	81%	40%
HR-	89%	53%
HER2+	95%	73%
HER2-	63%	20%
MP+*	91%	66%
HR-/HER2-	72%	34%
HR-/HER2+	94%	78%
HR+/HER2+	91%	65%
HR+/HER2-	39%	12%

Source: American Association for Cancer Research[20]

Table 4. The graduating arm is the HER2+/HR- subset with a 78% Bayesian probability of success in a 300-patient Phase III trial.

after three years, only 137 patients were randomized. An unblinded interim futility analysis indicated that the therapy was unlikely to demonstrate efficacy. Based on the analysis, the independent data monitoring committee recommended halting the trial. Early termination avoided unnecessary exposure for approximately 180 subjects.

Halting early avoids Phase III failures that contribute significantly to the low productivity and exorbitant cost of drug development, widely estimated at $1.8 billion per approved drug. A 2013 *Forbes* analysis suggests that for large biopharma companies—those that earn approval for eight to 10 new drugs over a decade—the greater number of failures experienced in managing a large pipeline result in an average cost of $5 billion per approval.[12]

Re-estimating sample size. Sample size is fixed in traditional designs, with size based on initial assumptions about primary efficacy measures and the rate and timing of patient withdrawal from the study. This approach often results in under powering or overpowering. In the first case, the study fails to show definitive results. In the second, the trial requires more subjects and time than necessary. Adaptive designs use interim data to re-estimate sample size as the trial proceeds, so sample size can be increased to ensure adequate powering.

The 2010 FDA draft guidance makes a distinction between blinded and unblinded adaptations to maintain study power. Blinded approaches, which FDA characterizes as generally well-understood, compare interim findings to assumptions used in the planning of the study. For example, in studies that use an event outcome such as response rate for the endpoint, a blinded examination of the overall event rate can be compared to assumptions used in study planning. If the comparison shows that actual event rate is well below the assumption, sample size can be increased. Such blinded approaches also can be used in studies using time-to-event analysis and continuous outcome measures. Since blinded approaches do not introduce statistical bias or require statistical adjustments, they maintain Type 1 error control. FDA recommends that they "should generally be considered for most studies."[4]

Unblinded approaches use interim analyses to estimate treatment effects. Unblinded approaches allow initial sample size to be increased if the size of the treatment effect is seen to be smaller than anticipated, but is still clinically relevant. In some cases, adaptations that address other elements of study design—such as dose, population, or study endpoint—could alter the study power and require re-estimation of sample size. Changes in sample size based on unblinded data analysis may cause an increase in the Type 1 error rate, and a statistical adjustment is necessary for the final study analysis.

FDA considers unblinded approaches to be less well-understood and cautions researchers to be conservative when making changes based on early estimates of treatment effect, which can be misleadingly large or small. Due to concerns about Type 1 error and operational bias, FDA suggests that unblinded approaches be used primarily for studies in which the primary objectives cannot be achieved using blinded designs. Drug developers exploring these designs must show adequate control of Type 1 error.

Seamless adaptive designs improve trial efficiencies

Seamless designs use adaptations and interim data to combine phases into a single study, reducing timelines and the number of patients required. These designs are especially useful in oncology studies because adaptations can address a wide variety of questions in the early (Phase II) stage to improve the later confirmatory stage. Seamless designs allow the long-term clinical endpoints from subjects enrolled in an early phase to be included in overall trial results.

Seamless Phase I-II designs. Seamless designs can answer Phase I toxicity questions and early Phase II efficacy questions in the same study. A simulated Phase I-II oncology study designed by Huang and coworkers demonstrates the efficiencies that can be gained using seamless approaches.[13]

The authors designed a parallel Phase I-II study that combined dose determination with efficacy assessment for two oncology agents when administered in combination, and when administered concurrently versus sequentially. The trial begins with an initial period of dose escalation. Then patients are randomly assigned to admissible dose levels that are compared with each other. Bayesian probabilities

are used to adaptively assign more patients to doses with higher activity levels. Combination doses with intolerable toxicity are eliminated, while those with lower efficacy are temporarily closed. The trial would be halted if the posterior probability of safety, efficacy, or futility crosses a prespecified boundary.

Applying this design to a combination chemotherapy trial for leukemia, the authors used simulations to compare the seamless Phase I-II approach to a conventional design with separate Phase I and Phase II trials. Results showed that the Phase I-II design reduced sample size was better powered and was more efficient in assigning more patients to doses with higher efficacy levels.[14]

Seamless Phase II-III designs. Larger Phase II studies can increase the probability of success in Phase III but also increase research timelines and costs. In many cases, Phase III success rates can be improved and overall timelines reduced using a seamless Phase II-III design that combines the learning-and-confirming phases into a single study. The first stage generates information to guide the confirmatory stage regarding decisions such as: whether to stop for futility; what dose, regimen, endpoint, and responding subpopulation to study; and whether to evaluate the experimental drug alone or in combination with another therapy.

Figure 2 (see page 33) shows a seamless Phase II-III design for a trial to evaluate two experimental drugs, alone and in combination, as adapted by Berry from "A National Cancer Clinical Trials System for the 21st Century."[7] In this example, the single agent, Drug B, is selected in Phase II and continues into Phase III. The number of patients and randomization in Phase II are chosen adaptively. Phase II results determine sample size in Phase III. Phase III may use interim analyses to halt early for either futility or expected success. Berry notes that the Drug B-versus-control element during Phase II may be counted in the Phase III comparison (i.e., inferentially seamless), or it may not be counted (i.e., operationally seamless). The entire trial must be simulated to control the Type 1 error rate.

Like the use of CRM in dose determination, the adoption of seamless designs in oncology studies is slow. When we broadened our keyword search of *The Oncologist* and the *Journal of Clinical Oncology* to include all trials at any phase of development, we found only three published studies (all in *Journal of Clinical Oncology*) that used adaptive designs between August 2012 and August 2013: two used adaptive randomization strategies, while one was a seamless Phase II-III trial.[14,15,16]

A 2012 survey conducted by the DIA Adaptive Design Scientific Working Group[17] suggests a considerable increase in the use of adaptive design, particularly compared to a previous survey conducted in 2008 (i.e., before the publication of the draft FDA guidance). The survey of 16 biopharma companies and CROs showed more enthusiasm overall for adaptive design within industry and academia, and in particular an increase in the number of trials using designs described as less well understood in the draft FDA guidance (i.e., typically more complex adaptive designs). The Tufts Center for the Study of Drug Development also showed that, based on a roundtable discussion held in 2013 with 40 senior executives,[18] across the industry simple adaptive designs (such as early stopping due to futility and sample size re-estimations) are used on approximately 20% of clinical trials and the adoption of adaptive design in the exploratory drug development phase is expected to increase significantly over the next several years.

Adaptive I-SPY 2 trial models a better research approach

The potential of adaptive design to advance oncology drug development is evident in the groundbreaking I-SPY 2 screening trial, a collaborative Phase II research platform sponsored by the FDA and used by multiple industry and academic researchers. I-SPY 2 is designed to identify active experimental drugs for breast cancer, together with predictive biomarkers.[5,19]

I-SPY 2 uses an adaptive design to simultaneously screen Phase II anticancer agents in women with stage 2 or 3 breast cancer at risk for recurrence. Drugs are evaluated by class, using standard and emerging biomarkers to measure their impact on pathologic complete response (pCR), a predictor of disease-free survival. Drugs considered successful in the screening trial are predicted to have an 85% likelihood of success in a confirmatory, randomized trial of 300 patients with tumors that have the drug's identified biomarker signature. The ultimate goal is to evolve a new model to streamline clinical evaluation and accelerate regulatory approval pathways.

The first two "graduates" from the I-SPY 2 trial are veliparib in combination with carboplatin and standard neoadjuvant chemotherapy in the triple-negative breast cancer subset, and neratinib in combination with standard neoadjuvant chemotherapy in HER2+/HR- breast cancer. Details of the clinical results and predictive probability of success are shown in Tables 3 and 4 (see pages 33 and 34).

Each drug's Bayesian predictive probability of success is calculated for each unique patient subset until the threshold of 85% is met within any given subset. When 85% probability of success is reached, the accrual is stopped within this subpopulation and the drug graduates to a separate Phase III trial within the defined subpopulation. While the published probability of Phase III success is greater than 85% for veliparib in the triple-negative breast cancer subset, neratinib's predictive probability of success was 78% at the time of publication.

The benefits of the I-SPY 2 trial are illustrated with the graduation of both neratinib and veliparib. Development

has been accelerated and focused on the patient population with the greatest probable benefit from treatment with the selected drugs, which leads to the greatest likelihood of success in a pivotal Phase III trial. Interestingly, without participating in this collaborative trial, these agents may have been in competition following traditional drug development pathways with a lower probability of success for each compound in a broader population. Having graduated in unique patient subsets, the compounds are no longer competing for the same patient population. This property of the I-SPY 2 trial enhances the development of multiple novel agents in breast cancer, which is increasingly recognized as consisting of many distinct sup-types of disease.

Conclusions

Regulatory guidance recognizes the value of adaptive design, and emerging research models like I-SPY 2 demonstrate its great value in advancing oncology drug development. It remains for the biopharma industry to implement and advance adaptive design as a fundamental clinical research methodology.

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The Evolution of Imaging Techniques in Clinical Trials

Ashwin Shetty, MD

Evaluating the use of new tumor measurement tools for studies of molecular-targeted cancer therapies.

The use of imaging has gained an increased role in monitoring tumor response to therapy. For many years, assessment of tumor response has relied on non-standardized, bidimensional measurements—World Health Organization (WHO) criteria—and now standardized technique measurements—Response Evaluation Criteria in Solid Tumors (RECIST). However, growing numbers of clinical trials are now using both diameter and volumetric measurements to assess treatment response, with the two kinds of measurements at times producing strikingly different results. In addition, we are now introducing metabolic and functional information from molecular imaging methods. Molecular imaging provides critical additional information for treatment follow-up of individual patients when used as a supplement to anatomic imaging.

Functional CT/MRI imaging

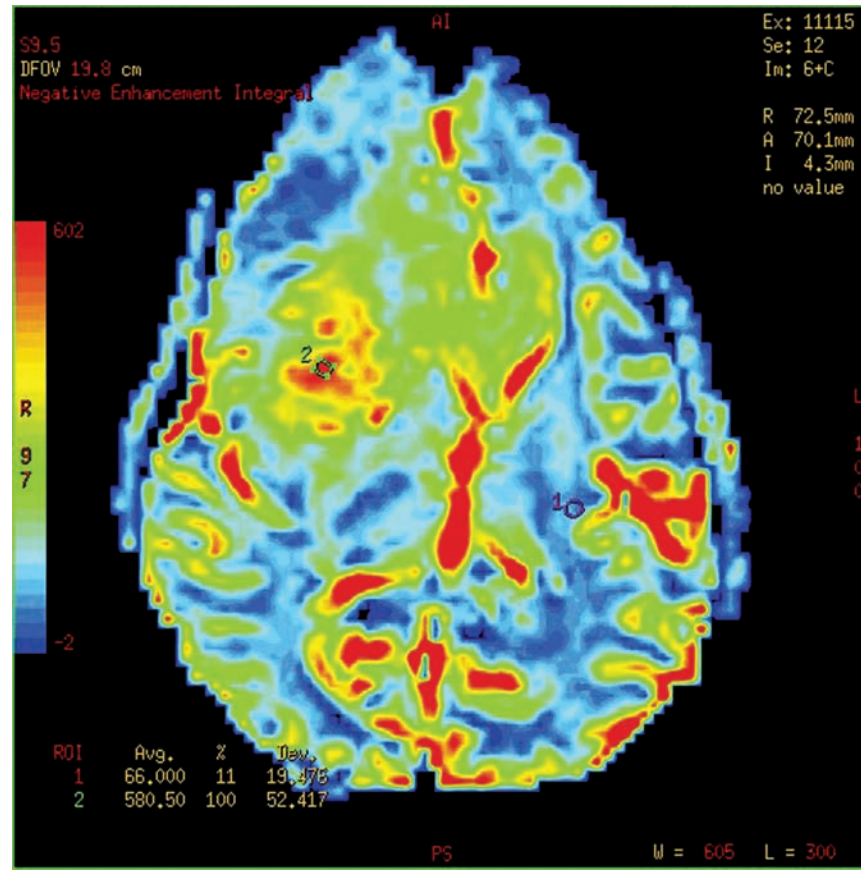
Transcatheter intra-arterial and molecular targeted therapies have proven to be valuable against primary and secondary hepatic malignancies. These therapies, which include transarterial embolization, intra-arterial chemoinfusion, transarterial chemoembolization with or without drug-eluting beads, and radioembolization with use of yttrium-90, inflict lethal insult to tumors while preserving normal hepatic parenchyma. Evaluation of treatment efficacy for all transcatheter-based therapies has been traditionally performed with radiologic measurement of tumor size as proposed by the WHO or RECIST Version 1.0 and 1.1 guidelines. Local therapies such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and transcatheter arterial radioembolization (TARE) with yttrium-90 induce cell death or necrosis. They may lead to stability of tumor size or even an increase in hepatic tumor size after therapy, a feature that limits the role of size-based criteria for assessing tumor response in this setting.

Similarly, molecular-targeted therapies may not change hepatic tumor size but cause alteration of cell growth signaling or alter the morphology of the tumor by affecting tumor angiogenesis. To evaluate the response of hepatic malignancies to therapy, quantitative functional criteria that are specific to tumor type and therapy have been developed. Examples include the Modified CT Response Evaluation Criteria for Gastrointestinal Stromal Tumors (Choi criteria), the European Association for Study of the Liver (EASL) guidelines, modified RECIST, and Response Evaluation Criteria in Cancer of the Liver (RECICL). Unlike anatomic imaging biomarkers, many functional imaging biomarkers demonstrate hepatic tumor response on the basis of tumor viability, which is assessed by measuring the residual enhancing tissue.

In 2010, a modified RECIST system was proposed. Modified RECIST quantifies the longest diameter of the enhancing part of hepatocellular carcinoma, which is assessed in the arterial phase of CT or magnetic resonance (MR) imaging and measured to avoid any major areas of intervening necrosis.

Positron emission tomography

PET Response Criteria in Solid Tumors (PERCIST) is a new criterion that may serve as a useful tool for assessing treatment response in FDG-avid malignancies, particularly those treated with cytostatic therapies. PERCIST is based on the change of the standardized uptake value (SUV) measurement within the tumor and the assumption that it provides a reproducible and reliable quantification of tumor metabolism. SUV should be measured within a 1-cm3 spherical region of interest (ROI) and be corrected for lean body mass (SUL). PERCIST adapts the RECIST 1.1 principles and measures the SUL peak in up to five index lesions (up to two per organ) with the highest FDG uptake. Response to therapy is expressed as a percentage change in SUL peak (or sum of the lesions' SULs) between the pretreatment and posttreatment scans. PERCIST classifies objective response in four categories: complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease.



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Perfusion MRI imaging of a malignant brain tumor.

Advanced cases of gastrointestinal stromal tumor (GIST) had limited therapeutic options until the introduction of imatinib, a tyrosine kinase inhibitor, which affects tumor cell growth signaling and has improved the prognosis of patients with this tumor. Studies have shown that use of tumor size alone to assess tumor response in patients with advanced GIST who undergo Imatinib therapy results in a significant underestimation, especially in the early stage of treatment.

In 2007, Choi et al. proposed new GIST-specific criteria that included evaluation of changes in CT attenuation in lesions after Imatinib therapy. They demonstrated good correlation between attenuation change seen at CT and tumor response seen at FDG PET. They also showed that some GIST lesions could even increase in size, despite clinical and FDG PET results indicating favorable patient response, a finding that emphasizes the limitation of size-based criteria. Tumor size may remain constant on CT, but nodules with increased uptake may be seen on PET scanning indicating residual tumor. Intra-therapy appearance of hot spots on PET indicate emergence of secondary resistance to therapy. Response to therapy can be seen as quick as 24 hours and this has shortened many clinical trials (e.g., sunitinib was brought to market six months ahead of schedule).[1]

Molecular imaging is useful in assessment of not only chemotherapy/biologic therapies, but also the monitoring of changes after image-guided intervention or radiation therapy. For example, PET/CT with fluorine 18 L-thymidine (FLT), a cell proliferation tracer, is being used in clinical trials to assess response to single-dose image-guided radiation therapy (IGRT). In a patient with metastatic squamous cell cancer of the oropharynx treated with IGRT, serial CT scans may show no change in the size of the metastasis. But just one day after treatment, FLT PET/CT scanning shows a decrease in the standardized uptake value and three weeks later there is a further dramatic response, and decrease in the standardized uptake value. A series showed uptake of FLT in all cases of head and neck squamous cell cancers and significant decrease in the first four weeks of chemoradiotherapy or radiotherapy. A greater decrease in 18F-FLT in the second week of treatment predicted a more favorable long term outcome.[2] Follow up with CT scanning on the other hand is usually done three to six months after radiation to differentiate recurrent or persistent tumor from radiation changes.[3]

Tc99 MDP bone scanning, which was for many years the mainstay for the evaluation of bone metastasis, can greatly

underestimate the extent of such metastasis. In patients with metastatic prostate cancer, three different studies are currently performed for evaluation of bone metastasis: Tc 99MDP scan, FDG PET/CT, and PET/CT with fluorodihydrotestosterone (FDHT), an androgen receptor tracer. The manifold increase in extent of bone metastasis and lymph node involvement that is detected at FDHT PET/CT but not at either FDG PET/CT or bone scanning shows the tremendous potential of modern molecular imaging for advancing cancer detection and follow-up post therapy. The most successful application for 18F-FDHT is a Phase I-II trial of the androgen receptor antagonist enzalutamide for castration-resistant prostate cancer (CRPC) reported by Scher et al. In a cohort of 22 patients, there was reduced 18F-FDHT binding after four weeks of therapy compared with baseline. This rapid evaluation of treatment is the power of molecular imaging agents and brings us closer to personalized medicine.[4]

On the horizon

Newer methods to assess tumor response based on volumetry, tumor vascularity, tumor cellularity, and tumor metabolism are on the horizon. Some examples of these newer methods include volumetric quantification of the whole tumor and necrotic component, diffusion-weighted imaging, tumor perfusion, MR spectroscopy, ultrasound, and MR elastography. Quantification by volumetry can be a more accurate reflection of the actual tumor size than uni- or bidimensional measurements. Linear tumor measurement has also demonstrated more inter-observer variation than volumetry in patients with hepatocellular carcinoma.

Apparent diffusion coefficient: The apparent diffusion coefficient (ADC) value, a diffusion-weighted imaging parameter, has been correlated with the tumor proliferation index and tumor grade before therapy, as well as with the presence of necrosis and tumor cell apoptosis after successful treatment. Studies have shown a potential to characterize malignant lesions and to differentiate viable tissue from necrosis on the basis of ADC cut-off values, because necrosis has higher ADC values. For patients with hepatocellular carcinoma treated with sorafenib, a transient decrease in tumor ADC value approximately one month after treatment has been reported to suggest hemorrhagic necrosis; however, a sustained decrease in ADC at three-month follow-up may indicate viable tumor or tumor progression.[5]

Impact on clinical trials

Imaging has secured a central role in evaluating the impact of devices and drugs in clinical trials. As the biomarkers described earlier evolve and become more specific and more sensitive, the impact on assessing changes in disease processes improves. This allows a new level of drug and device evaluation both at a functional and physiologic level. Specifically, for example, the utilization of the mRECIST criteria has allowed for a better understanding of response after interventional oncology treatments. Prior to the advent of these modified criteria, patients would have been disqualified after transarterial chemoembolization as their tumor size would often be unaffected after treatment. Under the new modified criteria, these patients would now be considered to have a positive response as the necrosis of their tumor would be properly characterized. As we continue to learn and evolve these methodologies, it will assist in ensuring novel therapies are evaluated appropriately.

In conclusion

In addition to size changes, various biologic and functional parameters can be quantified by using new imaging technologies. Measurement of these parameters is especially important for the evaluation of tumor response to newer targeted therapies, in which change in functional status sometimes precedes anatomic changes.

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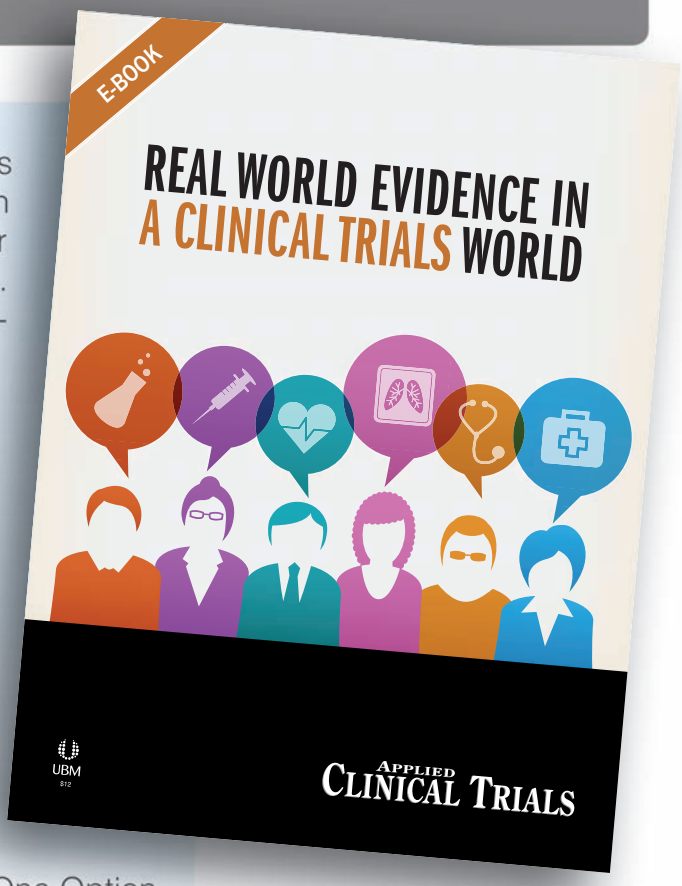

The Randomized Clinical Trial (RCT) is considered the gold standard of research and adds credibility to the efficacy or effectiveness of an investigational new drug. However, with a growing need for post-marketing safety databases, and increased need to collect qualitative information from patients in the pre- and post-market of a drug the evidence gathering from clinical trials onward is expanding. This eBook examines the growing trends of evidence gathering and how that impacts the clinical trials industry.

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Forecast Enrollment Rate in Clinical Trials

Gen Li, PhD

Building a structure for managing study operations through linking trial- and site-level forecasting.

On the surface, every veteran in clinical trials can tell you a lot about different factors impacting patient enrollment cycle times. A specifically defined patient population in a particular disease, for example, can impact the ability of sites to identify and recruit patients in a defined period of time, therefore, impacting enrollment cycle time. An experienced and successful investigator/site has better ability to enroll qualified patients compared to an inexperienced investigator/site. The higher proportion of experienced sites in a pool of sites deployed in a clinical trial can result in shorter enrollment cycle times.

Instinctively, when there are more investigators/sites being deployed for a trial with a defined number of patients needed, we should expect shortened enrollment cycle time. This sounds right, but is it really?

Here are two different scenarios:

- As clinical development organizations are under pressure to deliver new products faster, senior management seems happy to apply "unlimited" resources behind pivotal clinical trials evaluating promising drug candidates. The simple logic is to add more sites to the pool for enrollment, aiming to proportionately shorten enrollment cycle time. But realistically, how often does this shorten enrollment cycle time? The simple answer is: rarely, if at all.
- In another common scenario, when we are transitioning to a Phase III program after a successful Phase II program, we often "extrapolate" the operational results from Phase II trial(s) to Phase III trial(s); we use the enrollment rate from the Phase II trial(s) to calculate the number of sites needed for Phase III studies, hoping to achieve similar enrollment cycle times as we did in Phase II. That is all fine, except that the enrollment cycle time(s) will unlikely to be close to the calculation. The enrollment cycle times are generally substantially longer in this situation.

We have long noted that adding extra sites to a clinical trial has only limited impact to enrollment cycle time.[1] We naturally want a better, in-depth understanding of the issue—is there a pattern between the number of sites deployed and enrollment cycle time? If the answer is yes, is it possible to define that pattern in a simple and universally applicable mathematical relationship?

Interestingly, similar phenomena exist in other areas. When we track the growth of a school of fish, we find the average size of the fishes grows rapidly in the earliest days since their hatch. The incremental increase of their size diminishes at the same time segment was added. Eventually, the average size of these fishes will hit a ceiling; they will no longer grow in size.

Similarly, when we charge a battery, we can relatively quickly get to, for example, the first 50% of the battery being charged. The charge speed slows down, until it hits a ceiling at some point.

We know that the fish growth pattern has been thoroughly studied by ecologists, and the pattern to charge a battery has also been thoroughly studied by physicists. Could we possibly borrow

CTER Sub-database: Metabolic Disease Condition

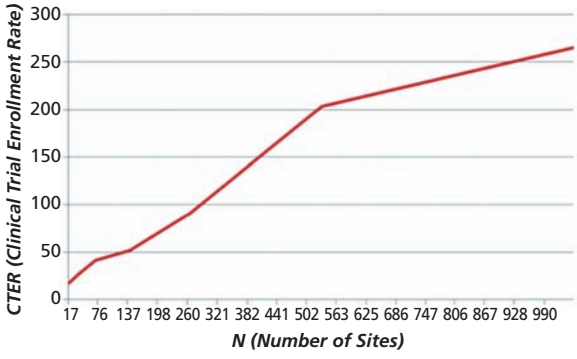

Figure 1.

CTER Sub-database: Respiratory Disease Condition

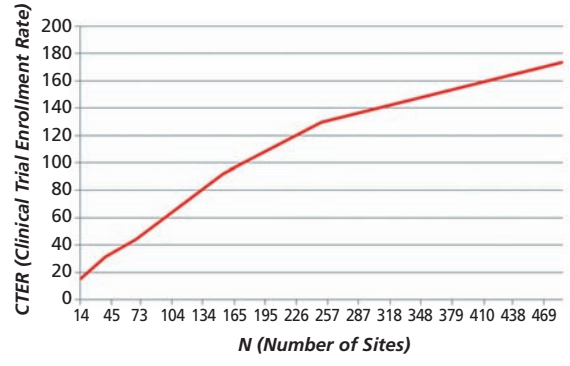

Figure 2.

what they have learned and apply it to understand the relationship between investigator sites and enrollment rates?

We know it is never easy to find any pattern in clinical trial planning and execution, for a simple reason: each study is distinctly different, and there is no such thing as two identical trials.

This article is a part of the author's integrated effort to build a conceptual structure for managing study operations in clinical development by focusing on forecasting enrollment rate at the clinical trial level (clinical trial enrollment rate, CTER) and site level (gross site enrollment rate, GSER). We are able to establish a relationship between the site activation process and site enrollment performance.

This article will also establish the relationships between these concepts. They are truly integrated components of an increasingly comprehensive conceptual framework.

CTER (number of patients per trial per month)

Using a clinical development database created by the author—a sub-database—the following inclusion criteria was established:

Sites vs. CTER

MEDIAN SITES (N)	MEDIAN TRIAL ENROLLMENT RATE (CTER)
17	17.9
37	26.8
72	41.2
141	51.8
264	90.8
534	203
1047	265

Source: Li

Table 1. Site totals and corresponding clinical trial enrollment rates.

Sites vs. GSER

MEDIAN SITES (N)	MEDIAN SITE ENROLLMENT RATE (GSER)
17	1.13
37	0.79
72	0.6
141.5	0.43
264.5	0.3
534	0.31
1047	0.29

Source: LI

Table 2. Site totals and corresponding gross site enrollment rates.

CTER Sub-database: Neurology Disease Condition

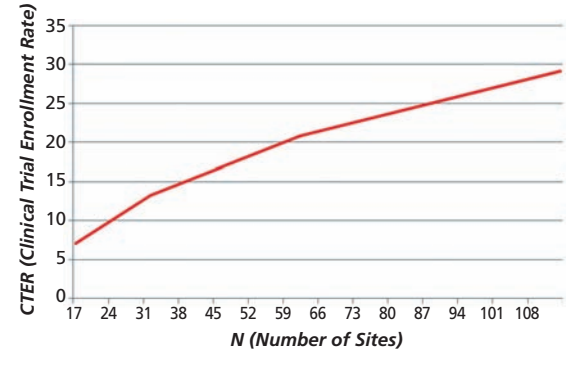

Figure 3.

- Interventional
- With 10 or more sites
- Started in year 2000 or later
- Completed enrollment at the time of analysis

And we excluded the following trials:

- Extension trial
- Registration trial
- Trials including healthy subjects
- Trials with expanded access

The sub-database of relatively "homogeneous" clinical trials for a single metabolic disease condition is illustrated in Figure 1. We took the following steps to derive this chart:

- Focus on trials with a single disease condition as primary condition
- Put the clinical trial into baskets according to number of sites: 10 to 25 sites, 26 to 50, 51 to 100, 101 to 200, 201 to 400, 401 to 800, and 801 to more
- Build a data table to pair median number of sites and median of CTER (see Table 1).

CTER Mathematical Relationship: Metabolic Disease Condition

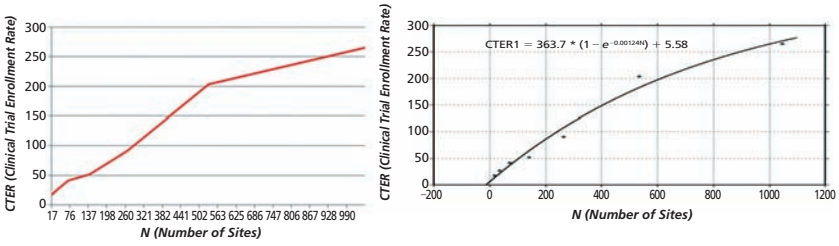

Figure 4

CTER Mathematical Relationship: Respiratory Disease Condition

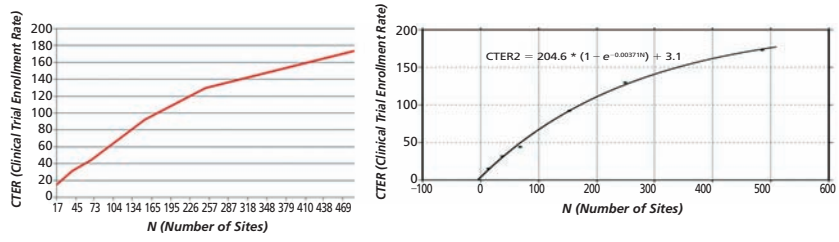

Figure 5

CTER Mathematical Relationship: Neurology Disease Condition

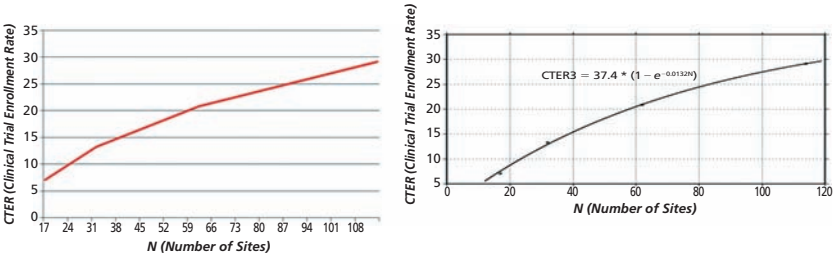

Figure 6

- Plot the data pairs in a chart

Going through the same steps, we can draw similar charts for trials in a single respiratory and neurology disease condition, respectively (see Figures 2 and 3 on page 43).

As a matter of fact, we can draw similar charts for a group of clinical trials in every single disease condition, when the sample size is big enough, and the disease condition is "pure" enough.

In each of the charts, we see a generalizable pattern: as more sites are added to a clinical trial in the same disease condition, the CTER increases. However, for every equal number of sites (N) added, the benefit to CTER diminishes. Eventually, the CTER will hit some sort of ceiling; the benefit from adding more sites becomes negligible.

The mathematics relationship is exactly the same relationship used to describe the growth rate for a school of fish in the ocean. Each of these charts seems to have distinct sizes and shapes. For the trained eyes of a mathematician, there is a simple equation to apply to the charts:

CTER = A * (1 - e^{BN}) + C, where CTER1 = 363.7 * (1 - $e^{-0.00124N}$) + 5.58. This equation is applied in Figures 4, 5, and 6.

From what we know now, there is no "proportionate" relationship between number of sites and CTER. That is to say, the relationship between sites and enrollment rate are not linear. With all factors equal, adding sites to a clinical trial can increase CTER, but at a diminished incremental benefit. Moreover, the benefit diminishes as more and more sites are being added.

In another words, there is an operational boundary where we have to plan and execute clinical trials within. When we keep adding sites to a study, we will hit the ceiling at some point, where there will be no measurable benefit in gaining enrollment rate. It is safe to say that there is a limitation in terms of how far we can go to shorten enrollment cycle time by adding investigator sites.

But why? If we were adding more sites to a trial relatively homogeneously, and assuming each of the sites behave in the same pattern as the others and do their job in recruiting patients for the trial, why can't their contributions be added up to give a "proportional" (linear) relationship to increase CTER?

GSER (number of patients per site per month)

The fact is, as we add more sites to a trial, participating sites can no longer behave in the same pattern as before. Simply put, the ability for individual sites to recruit and contribute patients is suppressed continuously as more sites are added to a clinical study, when other factors are equal.

Using the same approach illustrated to understand CTER, we can learn more about GSER. Starting from the same sub-database being used to understand CTER, we took the following step to build the chart showing the relationship between number of sites (N) and GSER:

- Focus on trials with a single disease condition as primary condition
- Put the clinical trial into baskets according to number of sites: 10 to 25 sites, 26 to 50, 51 to 100, 101 to 200, 201 to 400, 401 to 800, and 801 to more.
- Build a data table to pair median number of sites and median of GSER (see Table 2 on page 43).
- Plot the data pair in a chart (see Figure 7).

Going through the same steps, we can draw similar charts for trials in a single respiratory disease condition and trials in a single neurology disease condition (see Figure 8).

These charts have different sizes and shapes. But the pattern is relatively simple: as the number of sites used in a set of clinical trials for a single disease condition increases, GSER decreases. It is not a linear relationship. Rather, GSER drops much more quickly when the clinical trials involve a smaller number of sites. It stabilizes at a certain level when the clinical studies become big enough.

A shortcut is again used by utilizing the mathematical relationships behind this pattern:

GSER = a* e^{BN}) + C, where GSER1 = 1.10 * $e^{-1.93N}$) + 0.311. This equation is applied in the single metabolic, respiratory, and neurology disease condition trials in Figures 9, 10, and 11.

In the second scenario, as mentioned earlier, we cannot simply apply the site enrollment rate in a usually smaller Phase II clinical trial to a usually much larger Phase III trial. The GSER for a smaller Phase II study, when other factors are equal, is larger than the GSER for a larger Phase III trial. When we try to extrapolate the operational results from a Phase II clinical trial to a larger Phase III study, and use the GSER to predict the enrollment cycle time for the planned larger Phase III study, we end up with disappointing results. We will have longer enrollment cycle time, and often have to launch a "rescue mission."

GSER Sub-database: Metabolic Disease Condition

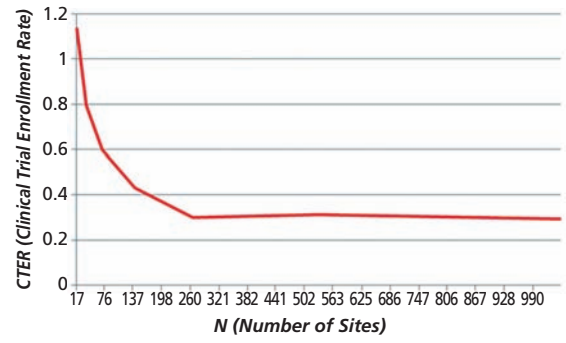

Figure 7

GSER Sub-database: Respiratory and Neurology Disease Conditions

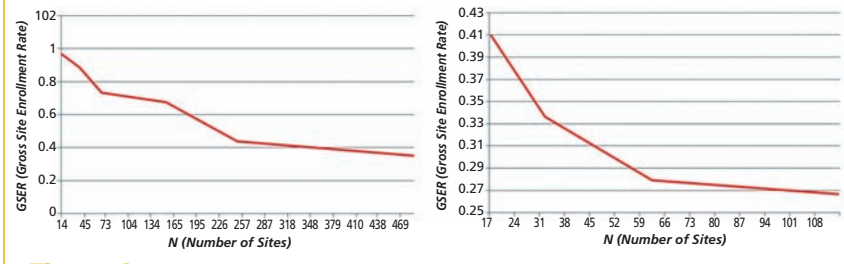

Figure 8

GSER Mathematical Relationship: Metabolic Disease Condition

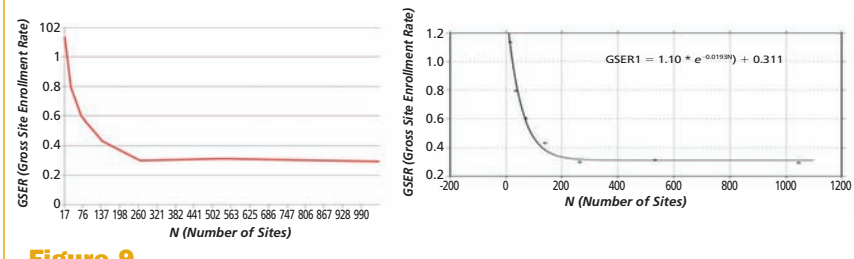

Figure 9

Discussion

As previously mentioned, there is no "proportionate" relationship between number of sites and CTER; the relationship between sites and enrollment rate are not linear. When other factors are equal, adding sites to a clinical trial can increase the trial-level enrollment rate, but at a diminished incremental benefit. Moreover, the benefit diminishes as an increasing number of sites are added.

Let's use Parkinson disease clinical trials as an example. When we plug in CTER=10 patients per month in the chart, we get N=24. When we plug in CTER=20 patients per month in the chart, we get N=58 (see Figure 12 on page 48). You can calculate the number of sites by plugging the CTER into the following equation without the aid of the chart:

CTER = 37.4 * (1 - $e^{-0.0132N}$)

When other things are equal, if we

GSER Mathematical Relationship: Respiratory Disease Condition

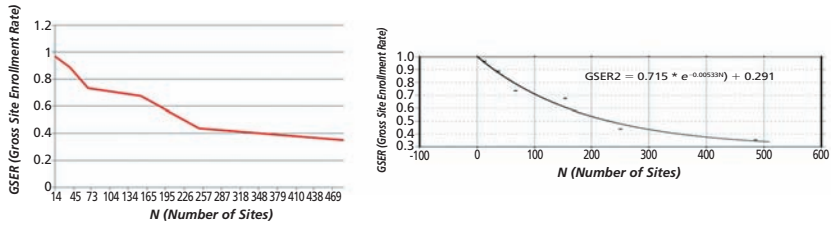

Figure 10

GSER Mathematical Relationship: Neurology Disease Condition

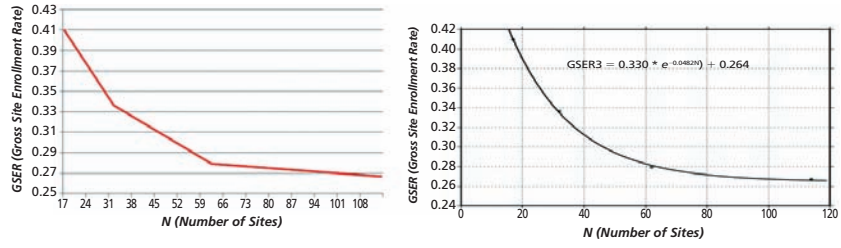

Figure 11

want to double the trial enrollment rate, in order to shorten enrollment cycle time by half, we need to add more than twice as many sites to the pool (58 sites instead of 48). It is important to note that this is just an example to illustrate the concept. In reality, it is not usually possible to cut the enrollment cycle time by half.

This established relationship on CTER not only helps to understand the operational boundary, but also to quantitatively define the marginal benefit from adding investigator sites, which in return will help to optimize the planning and execution of clinical trials.

In a recent project to assess operational feasibility for an early-phase oncology study, the author was tasked to recommend operational parameters and to forecast operational deliverables. By depicting the relationship between number of patients and enrollment cycle time, it became obvious that 10 patients per site would help minimize enrollment cycle time (see Figure 13 on page 48). For a 70-patient trial, we recommended that the team use seven sites. Using the method described in this article, we can establish the relationship between number of trial sites and GSER (see Figure 14 on page 48).

From the equation, we calculated the baseline enrollment rate (GSER) to be 0.2456 patients per site per month, and baseline enrollment cycle time to be calculated at 1,221 days. In our work, we continue to provide specific recommendations to improve the baseline enrollment cycle time through site enrollment performance improvement, business process improvement, site design optimization, etc. By using these approaches, it becomes feasible to shorten enrollment cycle time from 1,221 days at baseline to 705 days.

There are many factors that can be used to help us understand why larger trials have lower GSER than those of smaller trials. We established earlier that the enrollment performance for the pool of sites deployed in a clinical trial, as being measured by average site enrollment rate (ASER, number of patients per site per month), is impacted by the effectiveness of the site-activation process, which is measured by the site effectiveness index (SEI, 0% < SEI < 100%). With the introduction of GSER, we can use a simple formula to link all of them together:

GSER = ASER x SEI

As more sites (N) are involved in a clinical trial, operational complexity increases, which will lead to the decrease of SEI that, in return, will reduce the GSER.

> **When other factors are equal, adding sites to a clinical trial can increase the trial-level enrollment rate, but at a diminished incremental benefit.**

There is another more simple reason. While it is always difficult to find high-performing investigator sites, it becomes more difficult when we need to identify an even larger number of sites. It is not surprising that the average enrollment performance for a trial with a larger number of sites will be lower than studies that use a smaller number of sites.

Over the years, our efforts to help and support our colleagues in planning and executing clinical trials have been focusing on the following two objectives:

- Level the playground for stakeholders in clinical trial planning and execution. By doing this, we can improve the effectiveness of communication among stakeholders, and objectively reward those colleagues that achieved quantifiable improvements.
- Provide actionable opportunities to improve operational deliverables through better site selection, better process, etc.

Parkinson's Disease Trial: Site Level and CTER

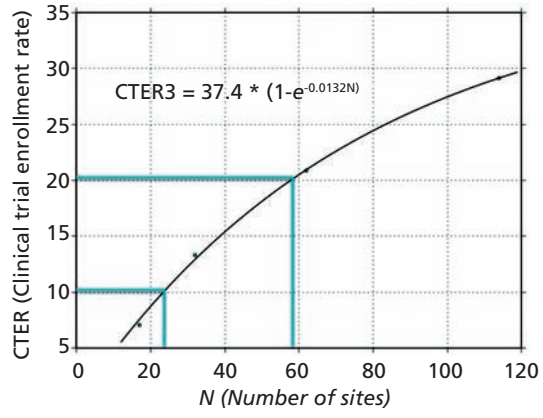

Figure 12

Oncology Trial: GSER Mathematical Relationship

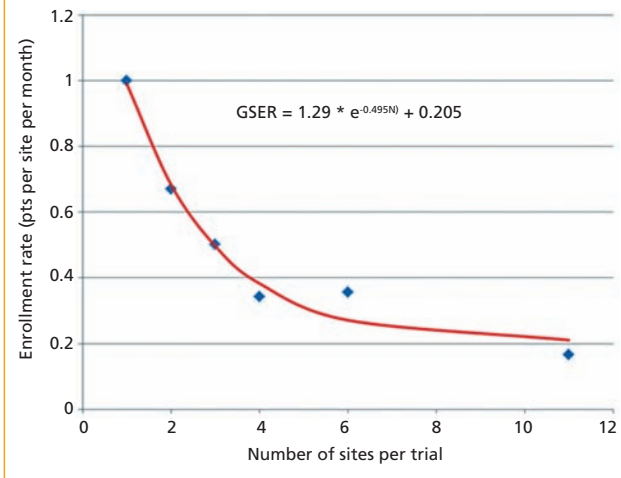

Figure 14

Oncology Trial: Patient Numbers vs. Enrollment Time

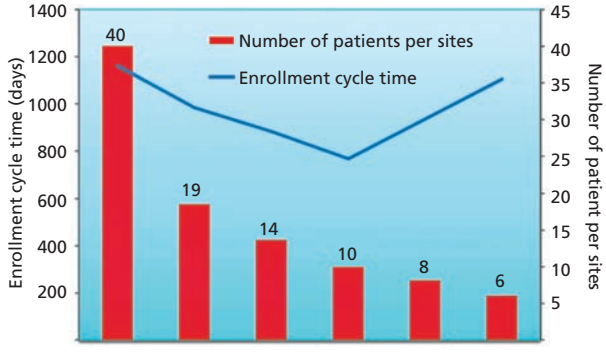

Figure 13

The establishment of a reliable way to forecast enrollment rate, both at the clinical trial level (CTER) and at the site level (GSER), will greatly enhance our ability to achieve our objectives. This is not to say that all clinical trials will and can fit in these equations perfectly. Quite the contrary; we know that most clinical studies will not be a perfect fit. But not only are we not discouraged by this fact, we claim that the "imperfect fit" is one of the most important value propositions of our method. We predict that the following factors will cause an "imperfect fit":

- A targeted age group too far away from "median" age group
- One or more biochemical and/or physiological and/or genetic measure(s) too far away from the "median" measures
- Targeted disease status too far away from a "regular" patient population
- Any other inclusion/exclusion criteria making the clinical trial too "unique"

While this is not an inclusive list, we are happy to say that our database is comprehensive enough to explain, often quantitatively, the impact from these factors.

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The Psychology of Cancer: Suicidal Ideation in Clinical Trials

Significant psychological effects, such as suicide ideation, are becoming critical points of measurement in quality of life outcomes.

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The need for robust and standardized psychiatric outcomes measures in clinical trials has increased in importance over the past several years. Biopharmaceutical enterprises are paying close attention to payer scrutiny in evaluating the value of new medical products, particularly in oncology and orphan disease indications. Governmental reimbursement authorities and payers are now requiring data that not only demonstrate the scientific value of a medical product, but also show improvements in a patient's quality of life (QOL) during reimbursement review.

Companies are touching on the notion of introducing clinical interventions during clinical trials, such as palliative care methodology, in order to better demonstrate the impact of their medical products in improving patient QOL outcomes. However, significant psychological effects, such as suicide ideation, are becoming critical points of measurement in QOL outcomes, and drug manufacturers are limited to very few validated psychological assessment systems.

Many patients experience psychological problems when they have been diagnosed with cancer, and undergo oncology treatment. Patients experience significant psychological effects from facing death, financial issues, emotional ties with friends and family, and adverse medical outcomes from oncological therapy. The psychological effects are so severe that some patients consider suicide. In fact, cancer patients are twice as likely to commit suicide compared to the general population. Sponsors are increasingly using suicidal risk assessment tools in their protocols after the release of FDA's suicidal ideation and behavior guidance document, which encourages sponsors to prospectively assess suicidal ideation in clinical trials, and recommends that they use the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trial design.

While these scales obviously ask patients about killing themselves, patients may not be truthful about their feelings of suicidal ideation due to fear that they may no longer qualify for an oncology trial, according to qualitative patient feedback. With emerging data from psychiatric treatment databases, researchers are now closer toward identifying suicidal patients through a variety of factors, such as religious beliefs, drug and alcohol abuse, marital status, sleeping patterns, and much more.

We analyzed psychiatric data on more than 2,000 New York City patients from Treatment Online, a validated online psychiatric platform that engages patients and clinicians. We have discovered statistical associations, which suggest that single people are more likely to have suicidal thoughts than those who are married, the stress of a relationship breakup (or death) significantly increased suicidal plan risk, and religious people are less likely to be depressed than atheists/agnostics.

Sponsors can leverage validated and licensed psychiatric scales in order to assess the impact and progression of suicidal ideation in cancer clinical trials. Moreover, study teams can use the aforementioned data analyses to not only develop predictive and risk models on suicidal ideation, but also create analytical benchmarks to improve sensitivity analyses.

This data can also benefit palliative care in healthcare settings and clinical trials, as understanding factors that affect suicidal ideation can impact intervention in palliative care. With regulatory agencies now starting to look at patient QOL perspectives in the approval process, pairing medical products with clinical intervention and palliative care during clinical trials can enhance therapeutic benefits.

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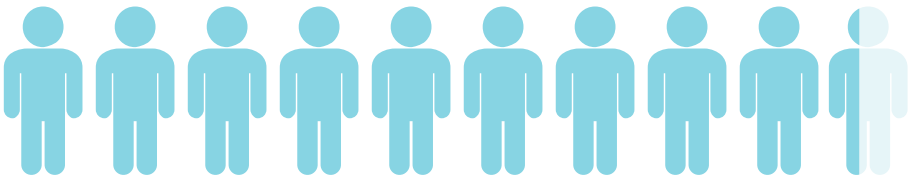

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