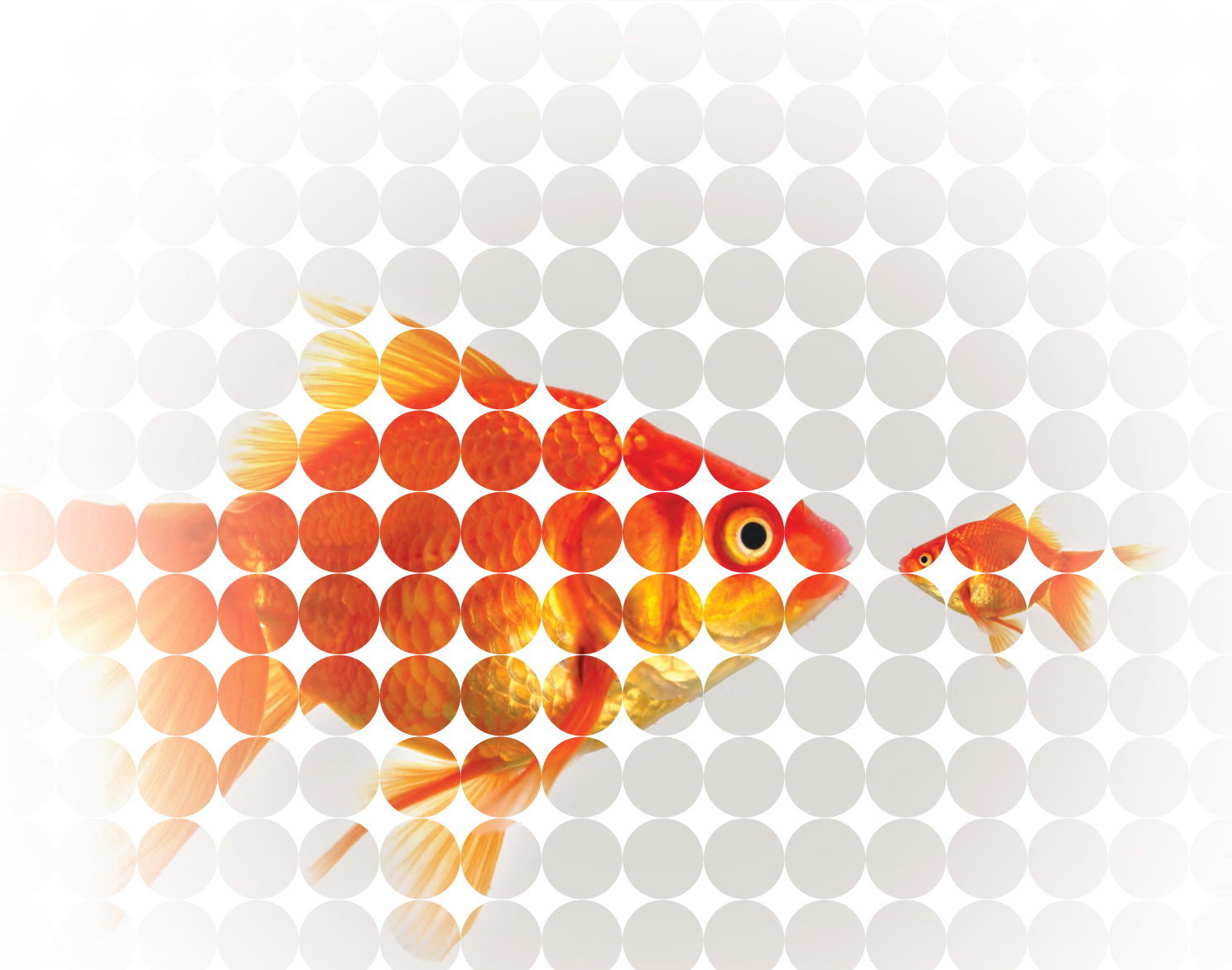

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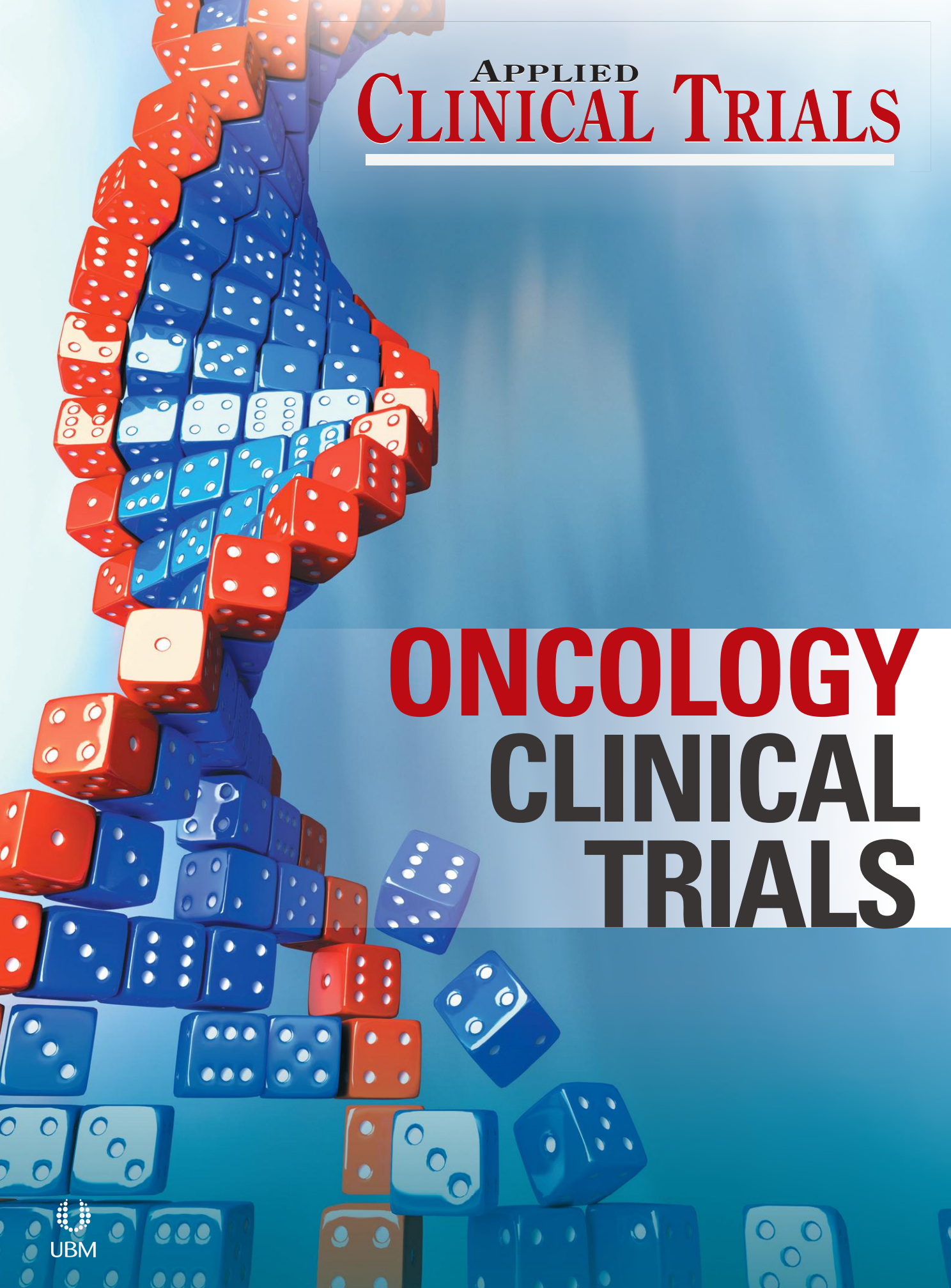

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Tackling Participant Protection in Complex Oncology Trials

The National Immunotherapy Coalition (NIC), under the Cancer MoonShot 2020 initiative, is accelerating next-generation immunotherapy as a viable treatment for cancer by establishing the most comprehensive cancer collaborative initiative in the nation. An expected 15,000 research sites will participate in the Phase II combination immunotherapy trials across the US as part of the initiative..

Cancer MoonShot 2020's Quantitative Integrative Lifelong Trial (QUILT), seeks to test combinations of therapies on up to 20,000 patients who have undergone whole genome, transcriptome and quantitative proteomic analysis. Under the direction of Dr. Patrick Soon-Shiong, M.D., Chairman and CEO of NantWorks, and founder of Cancer MoonShot 2020 is led primarily by the private sector and is focused on investing in the potential of combination immunotherapy as the next standard of care for cancer patients.

Academic cancer center and community oncologists will participate in the QUILT program, which will be stratified across multiple Phase I-III studies, addressing up to 20 tumor types including breast, lung, prostate, ovarian, brain, head and neck, and more. Pharmaceutical and biotechnology organizations have already committed to make more than 60 novel immunotherapy, targeted therapy and chemotherapeutic agents available to be combined across multiple tumor types based upon the results of this initiative.

"Novel therapies and study designs like those planned for the Cancer MoonShot 2020 program create unique challenges in protecting study participants," said Rebecca Rogers, Schulman IRB Chair and former member of Dartmouth College's Cancer Center Scientific Review committee and Gene Transfer Subcommittee of the Institutional Biosafety Committee.

Schulman IRB was selected as the national IRB for the historic Cancer MoonShot 2020 program and will be reviewing trials involving cutting edge therapies and innovative study design to ensure appropriate protections are in place for the participants.

> **"The IRB will work with researchers to ensure that potentially daunting, complicated consent content is made accessible and understandable to research subjects."**

"Cancer is an equal opportunity disease, and research professionals must ensure that those made vulnerable by socio-economic situations or by the disease itself are appropriately protected," Rogers said. "Individuals with life-threatening conditions, seriously debilitating illness or terminal illness may have a greater likelihood of being misled or manipulated when considering research participation."

Schulman's IRB membership includes multiple oncologists and research professionals experienced in oncology research, and will focus initial efforts on developing a comprehensive and consistent informed consent process. Oncology research consent forms are typically lengthy and complicated, using advanced scientific and medical concepts unfamiliar to even well-educated lay people. The IRB will work with researchers to ensure that potentially daunting, complicated consent content is made accessible and understandable to research subjects.

The consent process will address, among other things, the inconvenience of study participation and its foreseeable effects on the individual participant's quality of life, financial risk, data collection and use, and will ensure sufficient time has been built into the process for participants to consider their research treatment options. Financial risk is a major concern that will be addressed in the consent development process, with possible issues including being charged for non-standard imaging procedures, exceedingly high copayments, and insurance denial of payments.

Collection of biospecimens with associated genomic, epigenetic and phenotypic data is standard in oncology research. This collection and the possibility of future research will be carefully detailed in the consent form and reviewed throughout the informed consent process. IRB members will also consider whether potential study participants have sufficient time to process their diagnosis and prognosis prior to considering a research treatment option. Allowing adequate time for research team members to conduct initial and ongoing consent discussions with participants and their families will be an essential component.

"Informed consent is a process, not just a document," said Rogers. "Ongoing conversation and education is critical to ensure that participants understand the risks and benefits of the study, especially as those risks and benefits change over time."

Why Immunotherapy Works

The immune system is an ideal anticancer agent because it controls an array of diverse immune cells that have a high degree of specificity and the ability to distinguish minute chemical alterations. It also has a long memory, which means once a body develops immunity to a specific cancer, that immunity can last for up to several decades after effective antigen priming. Immunotherapy can also be delivered in various therapeutic formats.

One of the most exciting formats is checkpoint inhibitors, which work by releasing the natural brakes on the immune system so it can attack cancer tumors on its own. This is a game changing development that promises to have a huge impact on patient outcomes, because checkpoint inhibitors cause the immune system to target the tumor in real time, rather than waiting for lab tests to hunt down vulnerabilities in the tumor, which can change over time and delay treatment.

From a research perspective, immune checkpoint inhibitors are leading the way in clinical discovery and enthusiasm, given the exciting data yielded to date. As further research continues to elucidate the biology behind the antitumor immune response that is released by these checkpoint inhibitors, they are beginning to clarify why certain patients and indications may be more amenable to this class of agents, all of which helps us hone our ability to deliver precision medicine and improve outcomes for cancer patient worldwide. And while checkpoint inhibitors alone are good, there is much more work needed. Combining them with other immune therapies or more traditional methods such as surgery, radiation therapy, chemotherapy, and new therapies targeted at a specific mechanism is likely to be beneficial.

Regulatory agencies, including the FDA and EMA, are also showing significant interest in the potential of immunotherapy, further validating the impact of this treatment path.

Such advances are generating incredible excitement in the field of oncology,

Terry Murdock is Vice President, Head, Oncology Center of Excellence, at Quintiles.

Four Initiatives Driving the Future of Oncology Trials

Four recent initiatives directed at improving the way we conduct cancer research and commercialize treatments in the U.S. continue to make headlines. While there is still much work to be done, each of these initiatives has the potential to improve the often inefficient drug approval process, and reshape the way clinical trials are designed and conducted.

Precision Medicine Initiative

The decreasing cost of next-generation sequencing has enabled its integration into the clinical decision-making process, including within cancer research. It is common practice now to screen cancer patients for specific biomarkers to better evaluate and determine the optimum treatment for them.

The Precision Medicine Initiative was announced by President Obama in early 2015 to help realize this potential with the launch of the National Cancer Institute's MATCH Trial. This national, multi-site trial will take a new approach to patient recruitment on a larger scale than traditional cancer trials. Instead of stratifying patients based on their tumor type (i.e., breast, lung, etc.), the MATCH Trial uses next-generation sequencing to identify the genetic profile of an individual's tumor and stratifies patients based on their mutations. Using this design approach, known as "basket" studies, patients will be treated by medications known to target their specific mutations, regardless of tumor type.

21st Century Cures Act

The 21st Century Cures Act—designed to improve the discovery, development and delivery of new treatments and cures—passed the House overwhelmingly in July 2015, but has recently stalled with little movement. While the final contents and ultimate passage remain to be seen, the Act did generate increased momentum in Congress which has prompted the Senate Committee on Health, Education, Labor and Pensions to propose a number of bipartisan bills on issues ranging from expedited therapies for rare diseases and improving electronic health records.

Cancer MoonShot 2020

Cancer MoonShot 2020 was launched in 2016, and is a collaboration across pharma, community and academic oncology, government, and scientific communities to accelerate the potential of combination immunotherapy as the next standard of care for cancer patients.

National Immunotherapy Coalition

The National Immunotherapy Coalitionis specific to advancing cancer immunotherapy through collaborative efforts among formerly rival players within both large pharma and smaller biotech. The coalition will make possible access to over 60 novel and approved agents, and forms the basis for the trials under Cancer MoonShot 2020.

Rob King is COO of Novella Clinical.

Improving Oncology Trials Through Adaptive Designs

Dirk Reitsma, MD, Jürgen Hummel, Austin Combest, PharmD, Elizabeth Andrews, PharmD

Adaptive designs may address a number of research questions simultaneously.

Today's rich oncology pipeline—accounting for more than 28% of agents in clinical development—promises needed advances in cancer therapy.[1] However, only 6.7% of oncology agents entering Phase I clinical trials gain marketing approval[2], while only 34% of Phase III oncology trials published from 2003 to 2010 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 complexities of evaluating new targeted therapies add to this burden.

Adaptive and platform trial designs offer opportunities for improvement by shortening the time needed to answer key research questions, potentially 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 initially 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] The European Medicines Agency (EMA) similarly issued its Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design in 2007.[5]

The 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." The 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 I-SPY 2 breast cancer trial, a platform trial that uses adaptive design to streamline identification of active drug combinations and predictive biomarkers.[6] I-SPY 2 ("Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis") 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 development 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

The Key to Modern Clinical Operations

Cloud-based EDC technologies help reduce trial cost, complexity and duration.

Rising costs, increased complexity and low patient enrollment rates continue to hamper oncology-specific clinical trials and impede efforts to develop new cancer treatments. The good news is that technological solutions are dramatically reducing the burdens associated with trial management and simplifying participation for stakeholders.

Cloud-based electronic data capture (EDC), in particular, is creating significant benefits at each point on the trial continuum. With a central, web-based data repository, information is more easily shared and monitored, regulatory compliance is strengthened and costs are reduced.

Systemic challenges

Streamlining the trial process is essential to ensure that safe and effective medications continue to reach cancer patients as quickly as possible. The growing size and complexity of many trials, along with their increasingly global reach, has created new challenges in critical areas like data management, record keeping, stakeholder communications and regulatory compliance.

These difficulties are compounded by the continued widespread use of outdated legacy platforms and paper-based systems. Not only are legacy systems slower and more vulnerable to errors, many cannot accommodate new data collection technologies, such as mobile devices and wearables.

Problems associated with the current trial environment are contributing to soaring life-cycle costs for new drug development. Recent analysis by the Tufts Center for the Study of Drug Development found that the average cost of developing and gaining approval for a pharmaceutical was nearly $2.6 billion. The study put the combined mean cost for Phase I, II and III clinical trials at about $339 million.

Benefits of the cloud

Cloud-based EDC has evolved rapidly in recent years and today is helping organizations overcome systemic hurdles to reduce trials cost, complexity and duration. In essence, the technology creates a scalable, end-to-end study management platform that can be tailored to meet unique trial requirements. All activity–design, administration and general use–occurs through the same centralized web location.

A key benefit of this approach is ubiquitous and real-time data access. Relevant study information, including electronic case report forms (CRFs), patient-reported outcomes, PDF source documents, images, protocols and assignments can be captured, formatted, organized and accessed within the system.

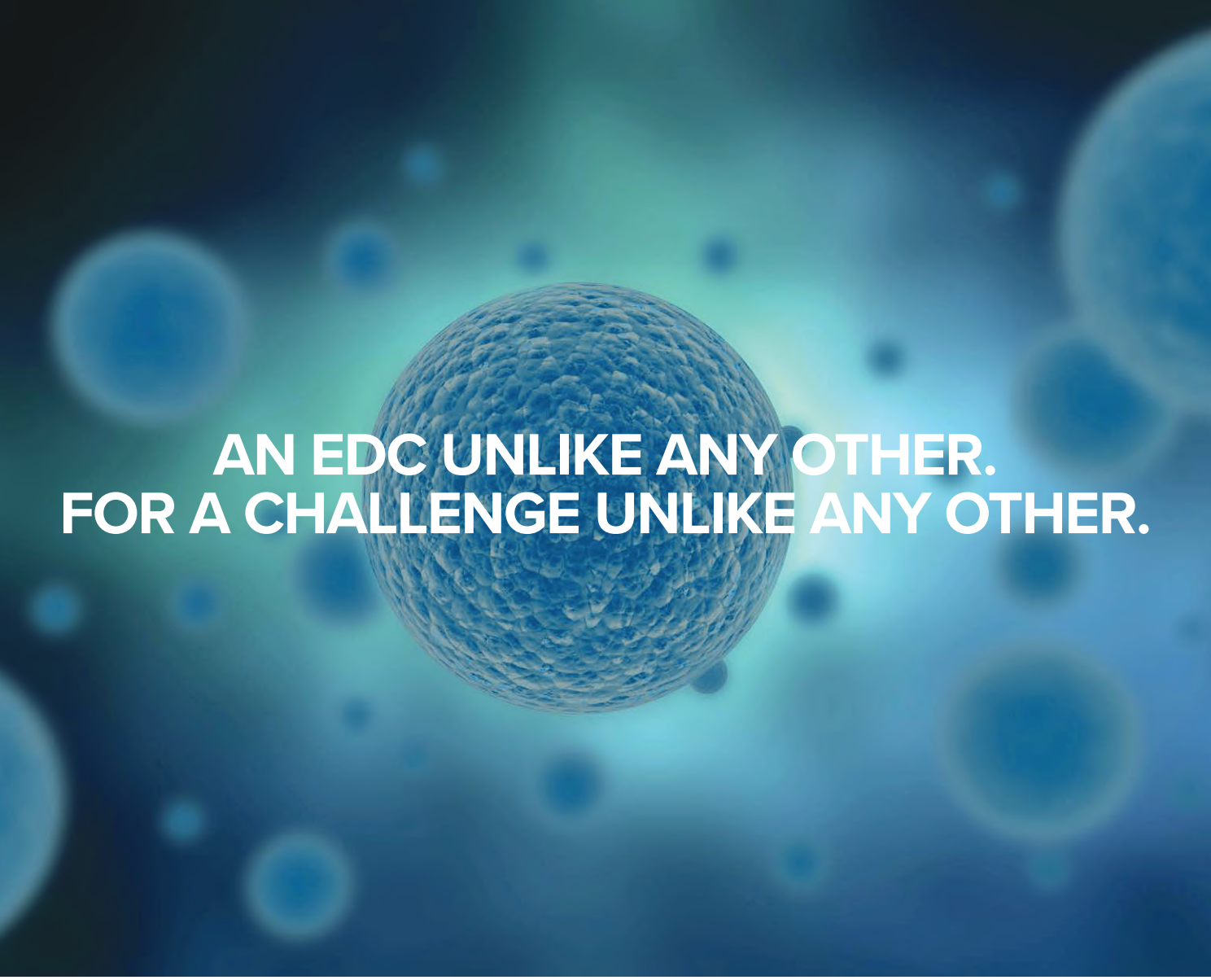
The instant availability of data from all sites allows investigators and managers to strengthen monitoring, reporting and regulatory compliance. In addition, cloud-based EDC systems typically provide a range of automated capabilities that further enhance execution and oversight. These can include complex query functionality; built-in error checks; role-based permissions, dashboards and visual metrics; full-system audit trails; secure hosting, back-up and disaster recovery; and automated archival. Applications also frequently include modular systems that perform essential tasks like streamlined adverse event reporting and automatic subject stratification and randomization.

Beyond enhancing data access and utility, cloud-based EDC enables more effective communication and collaboration between managers, staff, sponsors and patients. Information is instantly available and frequently more accurate. Built-in translation capacities mitigate language barriers between researchers across the globe. Team projects are more readily planned, executed and tracked. Communications are documented and searchable. And problems that do occur can be identified more quickly and addressed before they become significant.

The transformative power of technology

The benefits of cloud-based EDC applications mark a major step forward in rationalizing the complex and attenuated process of trial design, execution and fulfilment. EDC systems provide initial flexibility by allowing study designers to lay out broad trial parameters and then add details as answers emerge. Once underway, centralized trial data collection greatly enhances control, oversight and communications.

At the same time, robust functionality automates many of the tasks and steps necessary to bring a study to fruition. Taken together, these capabilities can significantly reduce both study costs and time horizons to help deliver effective cancer treatment products to the market faster and more efficiently.



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be incorrect at the end of the study. Faulty assumptions in Phase I and Phase II trials lead to 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 (Table 1).

Table 1. Performance Measures in Oncology Trials

Average Cost per Patient: Oncology vs. All Rx categories (2011)[7]
Phase I: $73,000 (vs. $36,000)
Phase II: $57,000 (vs. $47,500)
Phase III: $66,000 (vs. $47,000)

Overall Success Rates (2003-2011)[2]
6.7 % of Phase I oncology entries were approved
10 % of Phase I entries in all Rx categories were approved

Phase III Success Rates (2003-2010)[3]
34% of trials achieved statistical significant in primary endpoints

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, supporting better decisions at each sequential step. Adaptive approaches use early findings to improve the design of 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.

Roles of Bayesian statistics, simulation and biomarkers

Adaptive designs can incorporate more than one adaptation 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.[7]

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 on simulations to understand trial behavior, efficiencies, and risks as inputs 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 design[4], particularly if the data is intended to support a regulatory approval. Specialized simulation software, such as FACTS (Fixed and Adaptive Clinical Trial Simulator), is available to assess key performance characteristics including power, Type I error, bias, and average sample size.[8]

Table 2. Eight Common Types of Adaptations

- Stopping early (or late, i.e., extending accrual) with a conclusion of superiority of 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

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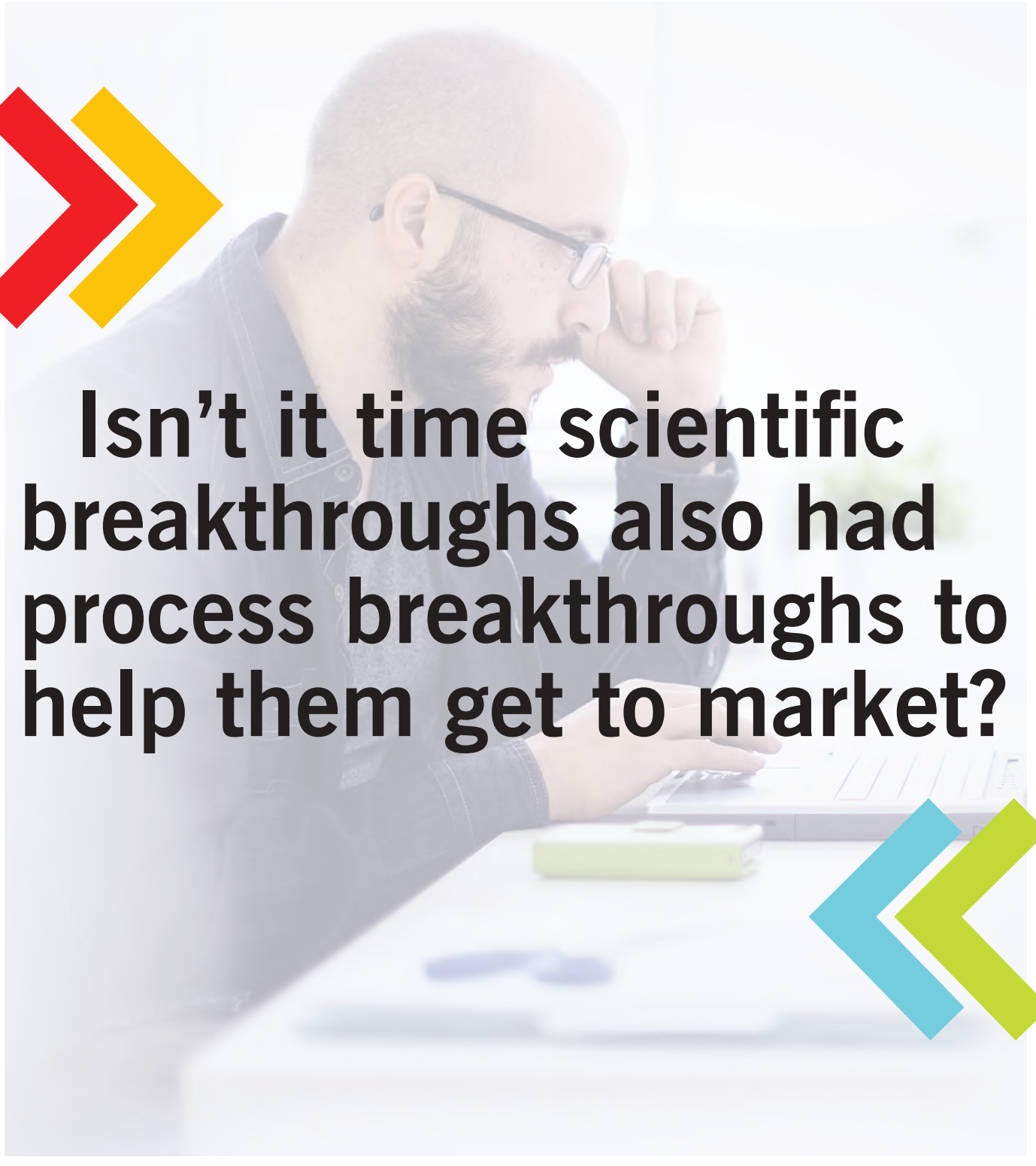

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Biomarkers provide early information. Biomarkers are important in adaptive designs to provide early measures of activity. Since early data may be used to modify a trial as it progresses, the traditional long-term oncology endpoints of survival and 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 end point … 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.[9]

Phase I dose determination improved

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, many of which identify MTD using a rule-based method such as the "3+3" design. An 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 enrolled at the next dose level. If one of the first three subjects experiences dose-limiting toxicity, up to three additional patients are enrolled at the same dose. If a dose limiting toxicity is observed in one of the added patients, enrollment stops and 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%."[10] 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.

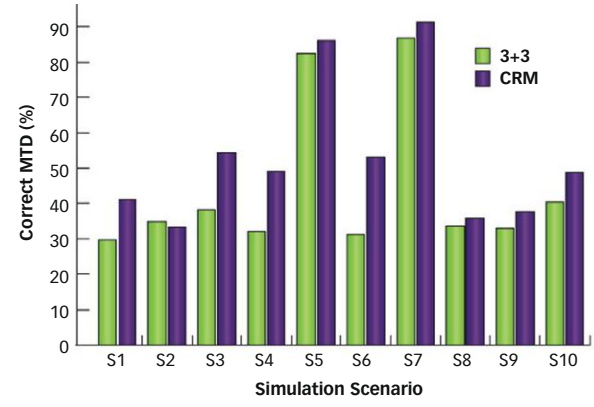
Adaptive CRM design. The continual reassessment method provides a better estimate of the true MTD. The CRM models the probability of the MTD as a function of dose level and continuously refines the probability. The 3+3 method bases the next dose allocation (and, therefore, the level that will eventually be declared the MTD) on the most recent 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 to a dose level, 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 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, the CRM was better than the 3+3 method 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 correct MTD than the 3+3 method. In Scenario 2, the CRM and 3+3 approaches yielded very similar results.[11]

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 cost of greater sample size."[11] 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 fa-

Figure 1. Correct Selection of Maximum Tolerated Dose (MTD)



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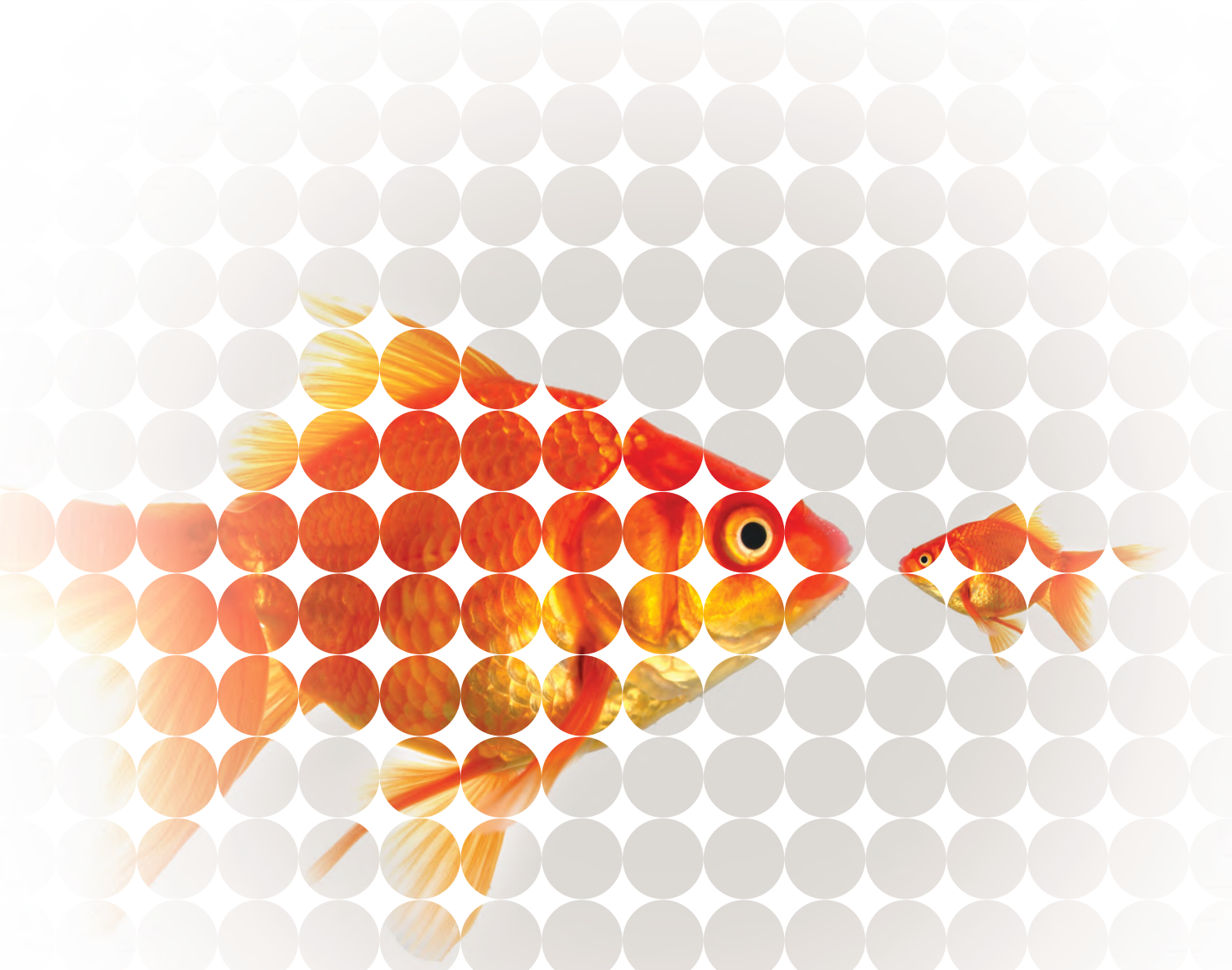

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miliarity. Our search using the key words "adaptive," "Bayesian," "CRM," "3+3," and "escalation" found a total of 11 Phase I and Phase I-II dose escalation trials published in The Oncologist (two trials) and the Journal of Clinical Oncology (nine trials) from January 2014 through January 2016. All but one of the trials used the 3+3 design, confirming the 2013 review by Riviere and coworkers, which reported "in 88% of trials, a traditional of modified 3 + 3 dose-escalation design was used."[11]

Adaptive approaches in Phase II improve Phase III trials

I*mproving 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.

I*mproving identification of target populations*. Increasing genomic knowledge of cancer subtypes is driving the need for efficient drug evaluation in targeted patient populations. 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.[12] 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.[6]

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.

H*alting 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 non-resectable glioblastoma multiforme. The target sample size was 323 randomized patients. Recruitment was difficult; 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.[13]

R*e-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 underpowering 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 the 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 the 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. The FDA recommends 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, making a statistical adjustment necessary for the final study analysis.

The FDA considers unblinded approaches to be less well-understood and cautions researchers to be conservative

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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, the FDA suggests that unblinded approaches be used primarily for studies in which the key 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.[14]

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 more efficient in assigning more patients to doses with higher efficacy levels.[15]

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 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."[8] 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 key word 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.[15,16,17]

A 2012 survey conducted by the DIA Adaptive Design Scientific Working Group[18] 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[19], across the industry simple adaptive designs (such as early stopping

Figure 2. Seamless Phase II-III Trial Evaluate Drugs: Alone and in Combination

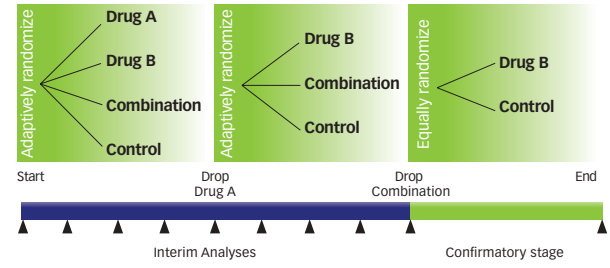

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Table 3. Bayesian Predictive Probability of Success for Veliparib

Signature	Probability Veliparib is superior	Predictive Probability of Success in a 300 Patient Phase III Trial
All HER2-	92%	55%
HER2-/HR+	28%	9%
HER2-/HR-	99%	92%

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

Table 4. Bayesian Predictive Probability of Success for Neratinib

Signature	Probability Neratinib is superior	Predictive Probability of Success in a 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%

The graduating arm is HER2+/HR- subset with a 78% Bayesian probability of success. (Reprinted with permission American Association for Cancer Research)

Table 5. Bayesian Predictive Probability of Success for MK-2206

Signature	Probability MK-2206 is superior	Predictive Probability of Success in a 300 Patient Phase III Trial
All	98%	69%
HR-/HER2+	97%	87%
HR-	99%	83%
HER2+	95%	78%
HR-/HER2-	97%	76%
MP+	97%	74%
HR+/HER2+	85%	61%
HER2-	95%	59%
HR+	82%	43%
HR+/HER2-	73%	32%

The graduating arm is the HER2+/HR- subset with an 87% predictive probability of success in a 300 patient Phase III trial.

due to futility and sample size re-estimations) are used on approximately 20% of clinical trials and that 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.[6,20]

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. To be considered successful, in the screening trial drugs must be predicted to have an 85% likelihood of success in this indication 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 three "graduates" from the I-SPY 2 trial are veliparib in combination with carboplatin and standard neoadjuvant chemotherapy in the triple-negative breast cancer subset, neratinib in combination with standard neoadjuvant chemotherapy in HER2+/HR- breast cancer, and MK-2206 in combination with standard neoadjuvant chemotherapy in HER2+/HR- breast cancer. These patient subsets are mutually exclusive and so were not in competition for regulatory approval. Details of the clinical results and predictive probability of success are shown in Tables 3, 4 and 5.

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 the three aforementioned drugs. 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 subtypes of disease.

Conclusion

Regulatory guidance recognizes the value of adaptive trial designs, and emerging research models like I-SPY 2 demonstrate the value of adaptive and collaborative designs 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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Engagement for All Approach to Oncology Trials

Cathy White

From physicians, to staff, to patients, a strategy of engagement will help recruitment and retention.

Global clinical trial performance and efficiency are being plagued by high turnover and noncompliance among principal investigators (PIs) and patients. According to the Tufts Center for the Study of Drug Development[1], while the highest turnover is observed among the least active investigators, turnover rates have been getting progressively worse among more active investigators. Moreover, despite thousands of trials and millions of cancer patients, less than 3%[2] of U.S. adults with cancer enter into a clinical trial.

Engaging physicians, sites, staff and patients in the clinical trial process is crucial in moving forward with new and effective oncology therapies. Accruing patients depends greatly on engaged, enthusiastic PIs, as they are the gatekeepers in helping patients decide to participate in clinical trials. Building staff awareness and enthusiasm are also essential for retaining participants. To improve identifying, enrolling and retaining patients, sponsors need to prepare and engage those administering the trial through a thoughtful and prudent resource approach, using the strategies that follow.

Planning for patients

Several factors are critical to the process of finding patients. First and foremost, sponsors should plan patient accrual and retention as part of a study's initiation activities as this information allows sponsors to better understand the realities of patient selection and enrollment patterns. Recruitment strategies must define the overarching plans to announce and generate interest in the trial as well as accrual and slot assignment processes for sites, so synergies can be maximized and adjustments made as the trial progresses. Similarly, plans must include strategies for fielding enrollment queries from out-of-region patients or healthcare professionals as may happen with online trial registries.

With about one-third of trial costs[3] stemming from patient enrollment across all therapeutic areas, understanding cancer prevalence within each geography and site is critical to successful site enrollment for oncology trials. A site's patient population and trial experience take on even more significance if the targeted cancer is rare or patient access is limited. Furthermore, a site's experience and capabilities relevant to a specific protocol may be difficult to discern, as not all countries or even regions within countries treat patients with the same cancer in the same way.

For example, variations exist between and within European nations in the diagnosis and surgical treatment for colorectal cancer patients and in the staging at diagnosis and subsequent treatment for breast cancer patients, according to the International Cancer Benchmarking Partnership. And while these medical differences were examined as part of an analysis of cancer survival, it is reasonable to extrapolate how such differences also impact the availability of cancer patients as potential trial participants.

To address these challenges, an experienced feasibility group can help. With access to local,

country-specific medical experts who routinely treat cancer prevalence and are familiar with standards of care, feasibility experts can accurately assess the type and size of patient populations a potential study site can realistically target.

Selecting sites

Planning how to accrue oncology trial patients will inevitably raise several site feasibility questions such as:

- How experienced is the site in this type of cancer and trial design?
- Is the site both adequately staffed and capable of accessing appropriate patients as well as the testing and sampling required?
- Will the site staff enthusiastically engage in the trial?
- What are the site's national, regional and local regulations?

Because trial protocols increasingly apply the latest technology to bring greater specificity to the research process, a site's ability to test for things such as patient-specific biomarkers as part of enrollment or trial monitoring can be as important as considering the site's experience with a particular type of therapy. Having in-depth, site-specific knowledge helps to efficiently manage within each site's standard operating procedures, including institutional contracting processes, scientific review board practices, ethics committees and data collection practices.

Engaging physicians

Accruing patients is also dependent upon engaged, enthusiastic PIs who understand and can champion the science of the candidate treatment to truly support a sponsor's trial and patient enrollment. However, the biggest hurdles physicians report for not participating in trials are perceived lack of time, responsibilities related to participation and compensation for work involved with screening, scheduling and managing patients. Also often cited is the intensity of paper work collection and filing as well as staff documentation training. Physician peer-to-peer communications cannot be underestimated in its importance in influencing physicians to join trials, as physicians are more likely to accrue patients if they are discussing treatment options with other physicians.

A study[4] presented at a past American Society of Clinical Oncology (ASCO) annual meeting found the use of direct physician-to-physician communications improved monthly accruals and increased enrollment 27.7% per site per month during a 15-month engagement and 16.3% during an 18-month engagement, respectively.

To facilitate these physician conversations, sponsors or CROs should prepare PIs both on trial specifics and likely questions from clinicians, staff and patients. Because of the dynamic nature of cancer science, ensuring PIs receive the peer-reviewed science supporting the candidate treatment helps to facilitate their understanding of the underlying scientific rationale of the investigational compound. This knowledge boosts PI interest, making the research more compelling and increasing the likelihood a PI will engage in trial discussions with their patients.

Because more than half of patient accruals in U.S. trials are drawn from community-based practices, PIs must proactively address concerns referring physicians may have about a trial. The greater the understanding referring physicians have of a trial and the ease with which they can follow the patient's progress, the more motivated they are to enroll patients. Understanding the referral physician network of sites is key to enabling sponsors to partner effectively to assure access to the broadest patient population.

Supporting staff

For sponsors outsourcing their trials, arranging for clinical research associates (CRAs) to be on location for first-patient enrollment provides additional support and reassurance while building staff awareness and enthusiasm for the trial. As the trial unfolds, CRAs routinely communicate and visit with site staff, help manage screening and enrollment logs, check patients' case reports, note the patients' calendars of events, facilitate enrollment and identify potential competing studies or responsibilities at the site. Trial managers can track site-specific patient flow and accrual, identify changes or trends and adjust the enrollment plans or accrual methods, either at individual sites or trial-wide through good trial management and a robust clinical trial management system.

Some organizations are implementing new technologies such as document exchange portals to support PIs and staff managing multi-site trials. Ideally, a CRA acts as an extension of the site staff team – someone with whom they can freely discuss any barriers to enrollment so together they can develop solutions.

Talking with patients

Physicians who "open the gate" to trials for patients need to do more than talk at a patient, they need to have a two-way conversation to achieve enrollment. Patients and their caregivers have many questions about research in general and the trial in particular and their first and most trusted source is their physician. Since many patients will not easily understand medical jargon, providing patient materials in lay terms fosters good communication and enrollment. Patient-focused trial materials may include posters, fact sheets and brochures.

Many oncology trials will require the accrual of women, underserved and minority populations and geriatric patients. For these groups, sponsors must recognize hurdles to trial enrollment, which include language, ethnic perceptions of illness and healing or cultural barriers of age or race. Notably, language and literacy are significant issues not just in initial physician-led conversations but also when acquiring patients' informed consent – extensive legal language in consent forms is known to decrease the desire to enroll.

Retaining enrolled patients

A variety of reasons exist to explain why patients stay for the duration of a clinical trial. Motivation can be a big factor for patients and site staff alike. When site staff use a variety of tactics to encourage patients, they have better results. The connections afforded by the Internet and social media appear to be ready made to help with trial communications; both to staff and to patients, yet many sponsors are still working on the most effective means to apply these tools beyond the use of trial registries.

Sending text messages to remind patients to take medications, make diary entries or get ready for a visit are other great ways to make patients feel more involved. For "science fan" patients, research updates have great appeal. Altruistic patients may appreciate recognition of their contributions to creating future treatments and standards of care. In more advanced trials where a new treatment may lead to significant delays in disease progression or regression, personal health updates take on even more significance to encourage patients.

To aid in peer-to-peer trial communications, password-protected web portals, separate from the formal trial operational and data management infrastructure could create seamless virtual peer communities where staff informally share recruitment tips, case studies, updates and experiences.

In addition to peer-to-peer staff communications, regular CRA communications build encouraging relationships with staff and help convey the importance of follow-up with patients before dropouts happen. CRAs can convey the encouragement and critical updates needed to keep a sponsor's trial top-of-mind, as competing trials and routine patient care also demand site staff attention. Regular onsite meetings permit a CRA to give site staff the trial progress as a big picture as well as site-specific activity. These connections also allow the CRA to acknowledge the staff's hard work and continue to foster positive relationships.

Conclusion

Regardless of the tactic, engaging sites, physicians, staff and patients in the clinical trial process are essential in moving forward with new and effective oncology therapies.

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Precision Enrollment in Oncology

Jeff Ventimiglia

New model pre-identifies patients based on study and biomarker criteria.

Today, three out of five oncology treatments are targeted therapies, with efficacy in only a small subpopulation of patients.[1] This drives higher screen failure rates and poses significant challenges for recruiting patients that fit a particular trial profile. Traditional models for targeting these sub-populations are time- and cost-intensive, making it difficult for oncologists to find the study that fits the individual patient.

In a new Precision Enrollment model designed by Quintiles, a network of more than 80 oncology centers across the United States is being built to speed up the recruitment efforts for cancer patients. An innovative combination of site networking, technology and process changes allows pre-identification of patients based on study and biomarker criteria, across broad geographic areas, using electronic health records (EHRs) and other data sources. Using a rapid start-up model, these pre-identified patients are then matched to the appropriate protocol. (Figure 1).

Pre-profiling right patient to the right trial

Pre-profiling is a core component of precision enrollment, which connects the right patient to the right trial quickly. This approach, which prospectively stratifies patients through genomic screening, provides value to both patients and clinical study sponsors. Patients are granted access to rapid, broad-based genomic testing of their cancer and clinical study sponsors experience faster recruitment of niche patient populations.[2] (Figure 2).

Streamlined site activation

In the precision enrollment model, the site is only opened after a patient has been identified, with site activation designed to take less than 21 days, a decrease in site start-up by over four months compared to the industry average for oncology trials.[3] Thus, zero-enrolling sites are reduced, while start-up and recruitment are rapidly accelerated. The site start-up burden is minimized during four key stages:

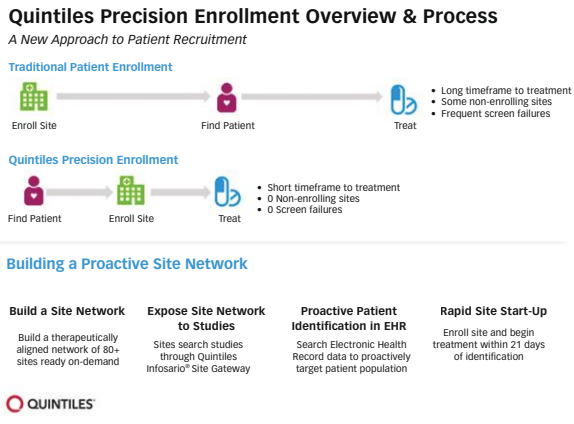
1. The site joins the network: At this stage, master services and confidential disclosure agreements are signed with the site, site profile documents are completed, and the site is onboarded to Quintiles Infosario® Site Gateway—an online portal which streamlines site start-up activities and helps alleviate the administrative burden on sites and investigators. By implementing standardized contracts and registration documents, this approach eliminates tedious site identification and the need for long-form feasibility surveys.

2. Studies are shared with sites: Here, many steps occur simultaneously, opposed to sequentially as established by traditional start-up pathways. Once the study synopsis is provided to the site and the site agrees to participate in the study, sponsor specific agreements are signed. At this point, a central Institutional Review Board provides a standardized informed consent form, review is carried out by Scientific Committees, and the study is shared with principal investigators (PIs). This allows for patient screening without opening the site.

3. Patients are proactively identified: During this step, patients can be identified through multiple channels: a historic review of site records, querying Electronic Health Records or biomarker screening. The PI screens patients based on inclusion/exclusion criteria, and the PI initiates study start-up by joining the study through Quintiles Infosario Site Gateway.

4. Rapid study site start-up is implemented: At this point, site start-up is designed to be completed within 21 calendar days. Study specific amendments are approved, IRB PI review is carried out, the registration package is completed, a work order is executed and treatment is administered.

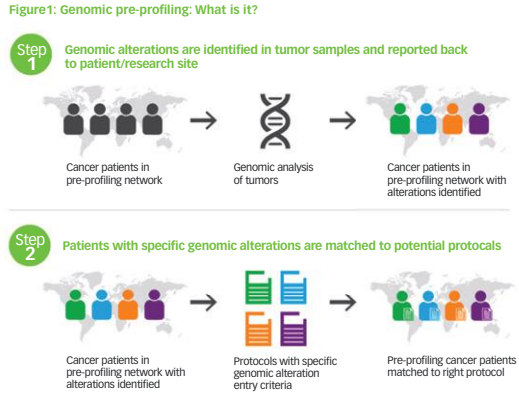
Quintiles' Precision Enrollment Overview and Process



Source: Quintiles, 2016.

Figure 1. In the precision enrollment model, the site is only opened after a patient has been identified.

Genomic Pre-Profiling



Source: Quintiles, 2016.

Figure 2. This approach provides value to both patients and clinical study sponsors.

Pilot study supports precision enrollment model

A small-scale pilot study targeting 50 metastatic colorectal cancer (mCRC) patients, sponsored by Quintiles, suggests that genomic profiling may increase clinical trial participation among cancer patients from the current level of 3% to 5% to as much as 35%.[4] This was due to treating physicians recommending a clinical trial in 35% of cases that reported actionable mutations.

The study enrolled and profiled 51 stage IV mCRC patients from July 2013 to October 2013 from 14 sites in the United States with turnaround time from sample submission to results averaged 15 days. Genomic variants associated with approved therapies in mCRC were found in 7.8% of patients, while 64.7% of patients had variants associated with approved therapies in other indications. A total of 84.3% of patients had variants linked with open clinical trials. Of these 43 patients, 32 had multiple biomarkers with associated trials.[2]

Importantly, the patients were not originally selected for clinical trial eligibility based on ECOG scores (used for measuring performance status, and developed by the Eastern Cooperative Oncology Group), life expectancy or organ function. This pilot suggests that there is potential to increase screening rates and shorten timelines for clinical trials by providing a broad genomic panel rather than using a single biomarker.

By speeding up recruitment, enabling rapid site start-up and reducing zero-enrolling sites, this first of its kind, end-to-end precision enrollment approach offers benefits to patients, sites and clinical trial sponsors alike. This is achieved by eliminating site identification and site selection visits, and completing multiple steps in the process in parallel, rather than in sequence as set by the conventional start-up pathway. This results in an interval designed to be less than 21 days between patient identification and enrollment in the trial.

Jeff Ventimiglia, Director, Site & Patient Networks, Quintiles

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Evolution of Value for Oncology Therapies

Thomas F. Goss, PharmD, Nicole Sweeney, Michael F. Murphy, MD, PhD

Common cancer therapy pathways provide value following an initial FDA approval.

In recent years, the United States has witnessed significant progress in the fight against cancer, with survival rates increasing from 49% in the mid-1970s to 68% today (R Siegel, et al., 2011; American Cancer Society: Cancer Statistics 2015). Improved therapies have contributed significantly to these advances in cancer care, with new medicines accounting for 50% to 60% of the increase in cancer survival rates since 1975. The progress driving these advances is commonly the result of an accumulation of knowledge over time, as a greater understanding of the biology underlying the more than 200 cancer-related diseases is accumulated.

Initial approval by the FDA is a significant milestone based on demonstration of a treatment's safety and efficacy, which are evaluated through carefully designed and controlled clinical trials, with research often continuing beyond FDA approval. Clinical experience is gained through post-approval research and the accumulation of evidence from the real-world use of oncology medicines in patients. While the intrinsic "value" (or clinical properties) of a therapy does not change, our understanding of the benefits and risks of the therapy evolves over time as evidence accumulates, resulting in significant interest in understanding the overall value of cancer therapies through this development life cycle.

Methods

We have examined this issue and identified a number of pathways that many cancer therapies have in common for providing incremental value following an initial FDA approval. We summarize these pathways with examples in Table 1.

Use within a singular FDA approved indication

In some cases, when patients are in need of new treatment options, the FDA may approve cancer treatments based on compelling surrogate endpoints (e.g., tumor shrinkage) before the completion of definitive long-term studies. The adequacy of the surrogate endpoint in accelerated or regular approval is also contingent upon other factors such as the size of the treatment effect, its duration, and the benefits of other available therapy available to patients. As clinical investigation of safety and efficacy continues, the impact on overall survival and tumor progression can be fully realized using the long-term clinical outcomes data, as demonstrated by the example of crizotinib.

Crizotinib (Xalkori®). Crizotinib was granted accelerated approval by the FDA in 2011 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that tests positive for the protein anaplastic lymphoma kinase (ALK). Approval was based on two studies that demonstrated that 50% and 61% of patients, respectively, experienced tumor shrinkage, indicating that the medicine was reasonably likely to predict a defined clinical benefit in these patients. In 2013, the FDA updated labeling to reflect the clinical benefit of crizotinib that had been proven through ongoing studies. Patients receiving crizo-

tinib experienced an average increase in progression-free survival of 7.7 months (time from randomization until objective tumor progression or death), which was more than double the three months of the chemotherapy arm of the trial.

Use earlier in treatment line and earlier disease stage

Because cancer is frequently progressive and life-threatening investigational therapies are necessarily tested first in patients with advanced stages of cancer, who have exhausted existing standard treatment options. Indeed, there is evidence that an increasing number of products in oncology are entering market with advanced stage indications. This creates a theoretical "ceiling" on the amount of clinical benefit that can be expected during initial clinical research impacting economic modeling which attempts to demonstrate value across a broad population of patients, disease severity, and indications. As additional testing is conducted following FDA approval, a therapy may demonstrate efficacy earlier in treatment line (when used prior to other available therapies) and/or disease stage (when used earlier in disease progression) as illustrated by the case of bortezomib.

Bortezomib (Velcade ®). Bortezomib was approved in 2003 to treat multiple myeloma patients who had received two prior therapies and were not responding (third-line therapy). In 2005 the label was expanded to include use earlier in the treatment regimen as a second-line therapy. Study data revealed that the time for the disease to progress was significantly longer in patients receiving bortezomib (6.2 months) compared to those receiving standard treatment (2.5 months). In 2008 the FDA granted approval for the use of bortezomib as a first-line multiple myeloma treatment after study results demonstrated that patients treated with bortezomib experienced significantly longer time to progression (20.7 months) compared to standard treatment (15 months). Ongoing research revealed the value of bortezomib as a first-line treatment, earlier in the progression of the disease, than initial results suggested.

Use in additional disease indications

Oncology therapies often have clinical value in cancers distinct from the original indication(s) for which they are approved. Studies conducted and reported after the initial approval commonly explore additional indications. Recent (pilot) regulatory considerations for the summary review of Supplemental NDA/BLA Submissions in Oncology may further accelerate approvals given the focus on only summary documents and trial reports. In many instances, a therapy demonstrates significant clinical benefit in a different disease as demonstrated by the case of lenalidomide below.

Lenalidomide (Revlimid®). Lenalidomide was originally approved in 2005 to treat patients with myelodysplastic syndrome (MDS) who had a specific genetic mutation. MDS is collection of disorders where the bone marrow fails to produce enough healthy blood cells. In clinical studies, patients treated with lenalidomide no longer needed blood transfusions. In 2006, lenalidomide received approval for use in combination with dexamethasone to treat patients with multiple myeloma who had failed other treatments (and in 2015 lenalidomide was approved as a first-line treatment). In 2013, lenalidomide was approved for use against mantle cell lymphoma, as the first oral therapy available for patients with this rare blood cancer.

Use in combination with other agents

Cancer research frequently involves investigating different combinations of new and existing therapies to improve outcomes. Combinations of targeted products may modulate different nodes in the same causal pathway for tumorigenesis, or impact parallel pathways with implications regarding patient

Table 1. Common Pathways of Cancer Therapies Following Initial FDA Approval

Use Within a Singular FDA Approved Indication	Use Earlier in Treatment Line and Earlier Disease Stage	Use in Additional Disease Indications	Use in Combination with Other Agents	Use in Combination with Specific Biomarkers
E.g., Crizotinib	E.g., Bortezomib	E.g., Lenalidomide	E.g., Everolimus	E.g., Ibrutinib
In 2013, the FDA updated labeling to reflect the clinical benefit of crizotinib that had been proven through ongoing studies	Originally approved in 2003 as a third-line therapy, approved for second-line therapy and 2005, and as first line in 2008	Originally approved in 2005 for MDS, expanded in 2006 to multiple myeloma, and in 2013 to mantle cell lymphoma	Originally approved in 2009 for RCC, expanded in 2010 for prevention of kidney transplant rejections and other indications in 2011 & 2012, with approval for use in combination with exemestane for breast cancer in 2012	Originally approved in 2013 for second-line treatment of Mantle cell lymphoma, added indication for CLL, approved in 2014, followed by approval for first-line in patients with 17p chromosomal deletion

Source: Goss, Sweeney, Murphy. September 2015.

segmentation, and the use of concurrent biomarker selection strategies. The use of combination therapies with targeted agents has often produced superior outcomes by enhancing anti-tumor activity by both allowing patients to receive a full-dose of drugs while managing adverse effects, and by attacking the tumor through multiple mechanisms of action to enhance response, expressed as either rate of response, survival rates, or duration of response, as illustrated by the case of everolimus below.

Everolimus (Afinitor®) Everolimus, a rapamycin (mTOR) inhibitor, was approved by the FDA in 2009 for the treatment of advanced renal cell carcinoma (RCC). In July 2012 everolimus was approved for use in combination with exemestane to treat post-menopausal women with advanced hormone-receptor positive, HER2-negative breast cancer. In this form of cancer, a class of medicines called aromatase inhibitors had proven effective at controlling tumors by depriving them of the estrogen hormone, which stimulates their growth. However, over time, many tumors developed resistance to these treatments. Everolimus helped prolong the effectiveness of these treatments by combatting that resistance.

Use in combination with specific biomarkers

Growing understanding of cancer at the molecular level has translated to new diagnostic tools that allow physicians to identify patients as candidates for a therapy based on the presence or absence of a particular gene or mutation (a prognostic biomarker). Biomarkers are used to predict therapeutic response and/or sensitivity to adverse events (a predictive biomarker), allowing clinicians to better select the patients who are most likely to benefit from particular targeted therapies. Ibrutinib illustrates this pathway below.

Ibrutinib (Imbruvica®). In February 2014, ibrutinib received approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have tried at least one prior therapy. In July of that year, FDA expanded the use of ibrutinib to treat patients with CLL who carry a deletion in chromosome 17 (17p deletion), regardless of whether or not they have received prior therapy. The clinical study resulting in this expanded indication demonstrated that patients with the 17p deletion who were treated with ibrutinib experienced a 75% reduction in the risk of disease progression and death.

Implications for clinical development design in oncology

Clinical trials of interventional oncology have transitioned from an exclusive reliance on measuring efficacy (effects within optimal patients at optimal sites), to assessments of effectiveness (clinical utility with representative patients and providers) toward efficiency (the economic value of the intervention). In part, this is a reflection of the diverse stakeholders present along the drug discovery/development continuum. Although the importance of acknowledging diverse perceptions is key throughout the discovery/development process, the relative importance attached to each stakeholder perspective has varied considerably throughout the phase of drug development and can be significantly modified by the therapeutic target. This environment substantively impacts trial design, study location, and methods of execution and analyses. For example, patients might be specifically interested in outcomes directly relevant to the most troubling sign or symptom of the presenting illness or side effects of treatment; while payers may focus on physician adoption, coverage, and pricing including reimbursement method. Correspondingly, the utility of various economic models used to estimate the value of innovative therapy may be limited, given the diverse spectrum of opinions which must be accommodated, and the differential importance given by patients to low probability, but high-impact therapeutic benefits generally obscured by population-based, and payer centric approaches (i.e., "hopeful gambles").

Given the increasing availability of alternative regimes (often both oral and physician-administered) oncologists often require data within their specific clinical care system to maximize obtaining estimates of healthcare utilization as the most directly relevant method of forming their clinical practice. The need for actionable data necessitates the creation of "micro-environments" within closed healthcare systems in which every physician-patient encounter can be captured. "Nested studies" within overall multicenter trials which focus upon overall healthcare utilization within a specific system or setting of care, while simultaneously addressing key primary and secondary study oncology objectives, provide one vehicle for addressing these specific needs.

Indeed, in a development program which must include studies covering the entire drug lifecycle, and potential transitions in patient disease severity, the planning for observational studies, including retrospective chart reviews, and longitudinal cohort studies best occurs at the end of first in human studies in which preliminary descriptions of product characteristics are available. Alternatively, international registries can be used to create single arm studies of efficacy and safety for patients not qualifying for controlled investigations, which ultimately complement data from randomized controlled trials. These trial designs collectively inform the type of data to be collected concurrently or within registration programs, and ultimately permit a more comprehensive examination of the clinical and economic value of new interventions at the time of product registration.

Conclusion

The healthcare environment is a mosaic of stakeholders, each with remarkably different demands for data addressing product attributes. Neither orderly, nor at times fully rational, these often conflicting perspectives require access to a portfolio of interventional and observational research designs to

effectively demonstrate the value of a novel oncology therapy in development to meet these often varied objectives and definitions of stakeholder value.

This dynamic is accentuated by the post-approval addition of new indications for marketed products; development of combinations of targeted therapies which introduce uncertainty into the regulatory process, pricing strategy and market penetration; the explosive growth in the need for both prognostic and predictive biomarkers which further fractionate the population where therapy eventually might be appropriate, and a need to accommodate the needs for increasingly granular data for a diverse audience. A business development philosophy which incorporates a strategic, rather than study specific view offers best prospects for addressing, in the proper sequence, hypotheses that are considered relevant to both regulatory approval, and eventual commercialization. Increasingly central in this process is the inclusion of observational studies launched in tandem and sequentially to required interventional trials, which provide insights from representative patients and representative practitioners and settings, who may be missing from traditional interventional studies encountered in the course of oncology drug development.

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