Volume 24 Number 2/3 February/March 2015

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Volume 24 Number 2/3 February/March 2015

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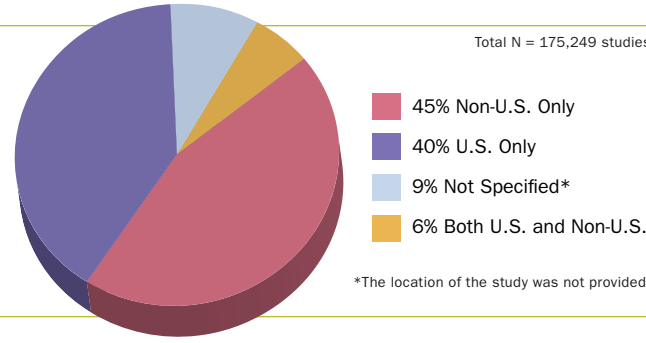

Source: ClinicalTrials.gov
The percentage of registered clinical trials by location (as of Sept. 23, 2014).

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CROs Can Use eTMF to Their Competitive Advantage

Contract research organizations (CROs) still using traditional paper or file-share systems to manage clinical documents throughout a trial expend great manual effort to maintain trial master file (TMF) quality and completeness—deeply impacting the relationship with sponsors. Since documents can be stored in paper and electronic format, there's greater likelihood of version control challenges—increasing compliance risk, process redundancies, and resulting in duplicate documents that require significant time and effort to reconcile at study close-out. The act of assembling trial documents into a coherent and readily accessible TMF has become an organizational drain for CROs and sponsors alike.

There's a better way. All stakeholders can benefit when using a shared eTMF application in the cloud that provides a single source during the study. All participants access the same documents and associated workflows, helping to increase visibility and control, compliance, and overall efficiency—ultimately fostering a trusted and lasting partnership between CRO and sponsor. Paperless TMF systems, easily and securely accessible by all in the cloud, remove barriers between sponsors and CROs to encourage trust and enable real-time information sharing. Almost half of the CROs surveyed report easier collaboration with sites (45%) and other CROs (49%) with paperless technology.

Visit bit.ly/1Hqaewz for the full version of this article

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VIEW FROM WASHINGTON

FDA Updates Policies to Continue Gains in New Drug Approvals

A surge in review activity at the FDA in December resulted in a near-record approval of 41 new drugs and biologics last year, the most since a record 56 approvals in 1996. A broader tally lists 54 new therapies by adding new drugs launched in Europe and Japan. FDA's total includes more than 15 orphan drugs and 15 first-in-class therapies, reflecting a continued industry shift to specialty drugs that can be developed faster, earn added exclusivity, and command high prices in an increasingly cost-conscious market. These trends support continued interest in developing drugs that qualify for breakthrough drug designation, which should continue to bring to market more new therapies for cancer and many critical rare conditions.

Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), would like to see more drugs studied in children, more anti-microbials, and more studies supporting additional indications for cancer therapies, she said in presenting a long list of priorities for 2015 at the December FDA/CMS Summit in Washington, D.C. Woodcock highlighted CDER efforts to post more information on participation in trials by sex, race, age, and ethnicity, and to improve drug development and clinical testing through broader use of Bayesian statistics and adaptive clinical trials designs and by further developing patient-reported outcomes measures.

Some of these topics are included in CDER's wish list of 90 new draft and final guidance documents in 2015. In addition to guidelines for approving new sunscreens and for establishing a supply chain drug tracking program, as required by legislation, the agenda proposes standards for developing drugs to treat alcoholism, Duchenne Muscular Dystrophy, head lice infestations, and ulcerative colitis. The agency also seeks more guidance on measuring treatment benefit in pediatric populations and on including pregnant women in clinical trials. And it proposes to expand electronic submissions, including information to support planning for bioresearch monitoring inspections.

FDA's review program benefited from improvements supported by the user-fee supported "program" for making the drug approval process more efficient and effective. John Jenkins, director of CDER's Office of New Drugs (OND), reports that more submissions are being evaluated in only one review cycle, saving time and resources for sponsors and for OND review offices. And two-thirds of novel drugs last year were first approved in the U.S.

Refining breakthroughs

At the same time, CDER is devoting considerable resources to handling the unexpected response to the breakthrough drug program and now is evaluating how to make the two-year-old initiative more efficient. The agency has vetted more than 200 requests for designations since January 2013, and has granted 70, generally to products that demonstrate notable clinical effect. The program has led to approval of more than 12 breakthrough drugs for several critical conditions, and dozens more are in the pipeline.

But a lot of work is needed to evaluate the two-thirds of breakthrough designation requests that are denied, which occurs most often for drugs with limited efficacy, tested in very few patients, or with flawed trial designs. To better manage the program, FDA is considering an abbreviated process for writing up rejection reports on "obvious non-starters." Further guidance will aim to clarify the "bar" for breakthrough requests, an issue that will be discussed at a workshop with the Brookings Institution in April.

Such a change could give agency reviewers more time to provide the "focused attention" needed to evaluate streamlined clinical trials and innovative statistical methods key to successful breakthrough drug development. Equally important is assistance in accelerating the manufacturing process and scheduling timely plant inspections for a drug likely to come to market much faster than expected.

FDA's efforts to bring more new drugs to patients has been noted on Capitol Hill, where Congressional leaders are looking to enact legislation this year to further speed the development of drugs and medical devices for unmet medical needs. The House Energy & Commerce Committee is considering a "discussion draft" for a bipartisan bill to promote "21st Century Cures," with a goal of moving it through Congress by summer.

At the same time, Republican leaders in the House and Senate will be airing proposals to "modernize" FDA operations with an eye to reducing what some agency critics describe as bureaucratic hurdles to bringing life-saving therapies to patients. Congressional oversight hearings are expected to press for faster response to compassionate use requests, streamlined approval of new medical devices and diagnostics, and more attention to patient perspectives in designing clinical trials and expanded access programs.

FDA officials hope that Congress also will provide additional funding to support the breakthrough program and other new initiatives that place added demands on staff. CDER currently has some 650 staff vacancies, many in review divisions.

— Jill Wechsler

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CLINICAL TRIAL OVERSIGHT

Pressure Mounts for Central IRBs

Efforts are escalating to encourage sponsors, research institutions, and clinical investigators to accept oversight for multi-center studies by central institutional review boards (IRBs), as seen in several discussions of this topic at the December conference on "Advancing Ethical Research" sponsored by Public Responsibility in Medicine & Research. The debate was heightened by the recent publication by the National Institutes of Health (NIH) of a draft policy promoting the use of central IRBs to make clinical trials more efficient. While regulatory officials, sponsors, and investigators acknowledged that oversight by multiple IRBs often is redundant, costly, and time-consuming, there remains reluctance by local sites and research organizations to hand the reins to others.

The proposed NIH guide "On the Use of a Single Institutional Review Board for Multi-Site Research," issued late last year, encourages participants in multi-site NIH-funded studies to use a single IRB of record. "Working through IRB review at each site can add delay without increasing the protections for research participants," NIH stated, noting that the National Cancer Institute (NCI) has had a central IRB in place since 1999, and other NIH Institutes have followed suit. NCI continues to encourage (but not require) investigators to utilize its CIRB review to reduce the administrative burden on local IRBs and investigators and to provide high-level protection for study participants. The new NIH policy acknowledges that foreign sites may not agree to central oversight, and that some exceptions may be appropriate.

Similarly, NIH's Clinical and Translational Science Awards (CTSA) program, which supports a large network of research sites across the country, is promoting the use of central IRBs for the review of multi-site research as part of its program to spur development of biomedical discoveries into new therapies. Patients are frustrated by the slow pace of clinical research and delays in trial start-up, noted Petra Kaufmann, director of the division of clinical innovation at NIH's National Center for Advancing Translational Sciences. She observed that the use of local IRBs at each site can delay study initiation.

— *Jill Wechsler*

REGULATORY REFORM

House 'Cures' Proposal Faces Tough Road Ahead

The "discussion draft" for legislation to speed "21st Century Cures" to patients emerged very quietly on Capitol Hill recently, muted by an absence of bipartisan support which had generated considerable enthusiasm for this effort to promote biomedical research and streamline regulation.

The massive document (nearly 400 pages) offered by House Energy & Commerce Committee chairman Fred Upton (R-Mich) includes just about every Republican reform proposal offered in recent years, including a number of changes in the FDA approval process likely to dismay agency leaders. Rep. Frank Pallone (D-NJ), E&C ranking Democrat, issued a statement expressing disappointment with the proposal, and Rep. Diana DeGette (D-Colo), titular co-chair of the Cures initiative, withheld her endorsement, but left the door open to reaching bipartisan consensus.

While analysts continue to examine the specifics of the draft plan, a general objection is that it offers no new funding to support the multiple programs and mandates added to FDA's already overloaded agenda. Similarly, numerous changes in National Institutes of Health (NIH) operations without expanded resources are generating protests from the research community. Health and biopharma organizations issued statements voicing the usual support for the effort, but clearly lacked enthusiasm.

More pointed protest came from the Generic Pharmaceutical Association (GPhA), which said it was "deeply disappointed" with proposals in the draft plan to boost market exclusivity for certain new therapies. GPhA predicted that these changes would erode generic drug utilization and savings by upsetting "the important balance between creating competition and encouraging innovation in the pharmaceutical marketplace." One area where there may be agreement is to use incentives to spur development of antibiotics, a goal championed by all sides and recently backed by President Obama. And some generics makers could support a provision offering extended exclusivity for "American-manufactured" generics and biosimilars.

The something-for-everyone document contains several provisions to revise clinical trial operations (revise human subject protections) and research methods (encourage adaptive trials, Bayesian methods). Compassionate access to not-yet-approved therapies for severely ill patients also gets a nod. Here, the legislators want to require pharma companies to be more "transparent" regarding expanded access programs and look to a new task force to recommend further reforms of FDA's expanded access process.

— *Jill Wechsler*

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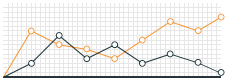

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After a five-year review of clinical trial quality measurement research and practices, we have concluded that clinical trial quality measurement does not meet current scientific standards. This creates an uncomfortable situation in a $71 billion industry: trial sponsors and managers must depend on indirect indicators to know the quality of their clinical trials. This lack of scientific quality measurement contributes to industry's struggles to address problems like cost overruns and adherence to timelines. Effective clinical trial management and improvement can only happen if there are valid and reliable (i.e., scientific) quality metrics. More information on the research and findings can be found at: http://bit.ly/1CeggPz.

The challenge of measuring quality

One of the major obstacles to achieving scientific quality management is an understanding that clinical trials, as a service, are fundamentally different from measuring product quality. So while the quality of a manufactured pill can be assessed with the usual operational metrics, the quality of conducting a clinical trial requires a different approach to measurement. The differences between products and services that have the greatest impact on measuring service quality are intangibility and heterogeneity. First, services are intangible—they lack objective attributes that can be directly observed. In measuring clinical trials, then, we need to depend on evaluations from specific expert witnesses, meaning a move to purposive instead of random sampling. Second, services are heterogeneous. Each clinical trial is different from previous trials.

This creates a couple of problems: If every trial is different from all other trials, how do you create standards for performance and who gets to decide if they meet the standards? The customer—or in the case of clinical trials, the sponsor or patients—have the prerogative of evaluating the trial because they are the ones who are in a position to judge the value created and adjust expectations to the context. While there is an intuitive appeal to adopting manufacturing approaches to measuring quality and performance, clinical trials are services and not products. Since services and products are fundamentally different, applying manufacturing measurement to a clinical trial service is not appropriate.

Research focus

The purpose of the larger paper was to assess the overall quality and performance in clinical trials using scientific measurement methods. This research results from a collaboration between CRO Analytics, Drexel University, and *Applied Clinical Trials*. This research was conducted in two phases. Phase 1 was the establishment of a qualitative methodology based on input from industry experts on performance and quality drivers of trials. Our subjects broke down performance activities into four distinct stages: sales & contracting, study startup, conduct, and closeout. Phase 2 was a quantitative study in which we purposively sampled experienced industry executives in an online survey solicited through our contacts, industry association appeals, and outreach to *Applied Clinical Trials* subscribers. There were 300 respondents who evaluated the overall performance of an individual stage of a trial in which they had recently participated.

In presenting our data approach at conferences, we encounter people who prefer operational data because they are "more objective." As we have shown, attempts to use operational data as a service quality measure is fundamentally and logically flawed because they fail to account for the differences between manufactured goods and services. Secondly, objective data, especially operational data, typically lack validity as quality indicators. For example, the number of days it takes to recruit patients. "Days" is a measure of time—not quality. Whether or not 76 days to recruit patients is high performing depends on the individual trial, so it lacks validity as a quality measure. Thirdly, these assessments are evaluations, not opinions. Finally, the measures we describe here all meet the statistical standards for validity and reliability. We are not aware of any operational metrics that can meet these basic scientific standards.

Results

We received 300 responses assessing trials in the U.S., Europe, Russia, India, China, Japan, other Asia, and South/Central America. The average number of subjects was 1,068 per trial and the average number of sites was 97. Study results included:

- The average quality and performance scores were lower that we expected. There was considerable score variation.
- Quality varied by the phase of the trial, with performance being highest in Phase II and lowest in Phase IV.
- Quality varied by the number of subjects and sites.
- Performance was lowest in study startup, while conduct and closeout had the highest performance scores.
- Performance also varied by the number of subjects and sites in the trial, but in a different pattern compared to quality.

The study results raise concern not only for the average quality of clinical trials but also the variation in quality. In order to begin to address these concerns, it is critical that we adopt scientific measurement approaches that have been adopted across most other service industries.

—Michael J Howley and Peter Malamis

VIEW FROM BRUSSELS

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Does the Adaptive Pathways Debate Go Far Enough?

While discussions have advanced in Europe, two key omissions from the dialogue may limit any real change

Momentum is gathering in Europe's attempts to open up alternative pathways for innovative medicines to reach patients. At the end of 2014, the European Medicines Agency (EMA) presented a report on the pilot program it has been running since last March, which demonstrated growing industry interest in taking part, as well as some first concrete steps at exploring methodologies. EMA said that it had received 34 requests from companies to include ongoing medicine-development programs—a significant boost to the scheme. Because of the initial cautious response by companies to its invitation to propose experimental medicines still in the early stage of clinical development, agency officials felt constrained during the year to issue renewed invitations almost in the form of a plea.

Closer collaboration sought

The pilot is exploring the challenges that the agency's approach presents—and particularly how to achieve close collaboration among key constituencies: health technology assessment (HTA) bodies, organizations issuing clinical treatment guidelines, payers, and patient organizations. Support for product development is envisioned in the form of guidance to applicants from early dialogue and planning for strategic collection and use of real-world data. EMA says the pilot "provides a framework for open and informal dialogue between stakeholders, allowing them to explore different options in a 'safe harbor' environment and to consider detailed technical and scientific questions based on concrete examples." It is not concerned with evaluating data and results. It is simply testing out procedures and ways of formulating development plans.

Discussions abound

For some companies, guidance is already emerging—or, at least, steps have been taken in preparation to provide guidance. During December, the quality aspects of an advanced-therapy medicinal product were examined in a face-to-face exchange between the company, the agency, HTA bodies, and patients' representatives. The discussion involved members of the agency's committees for medicinal products for human use and for advanced therapies, and of its scientific advice and biologicals working parties. By mid-December, the agency had also held one-hour teleconferences with seven applicants, and six medicines have so far been selected to go forward to the second stage of in-depth face-to-face discussions. Meanwhile, a teleconference took place between EMA and HTA bodies from the UK, the Netherlands, Sweden, Italy, Austria, and Germany, to discuss how product-payment might be integrated into the pathway.

Pilot specifics

The drugs selected for the pilot so far come from companies that have been able to show how they aim to take advantage of the adaptive pathways approach—how they will argue the merits of the product with HTA bodies, how they will gradually expand indications or populations, and how they will incorporate real-world data into the post-authorization evaluation. But confident that it now has sufficient candidates, the EMA will tighten up its selection procedures starting from the end of February, and accept only "very well-developed proposals, which include scenarios requiring input from different stakeholders"—by which it means HTA bodies.

However, there are two crucial elements that are still missing from the pilot—and indeed from the European efforts to examine the merits of adaptive pathways. One is that, quite explicitly, the EMA pilot is focused uniquely on making the best use of existing regulatory tools. In other words, it is deliberately shying away from any reflections on what might be done with a shift in the European rules on medicines authorization. Politically, that is understandable. In a Europe that is laboring to find consensus even on how to dig itself out of recession, austerity, and deflation, or to respond to Russian aggression on its borders, or to cope with hundreds of thousands of desperate irregular migrants, the chances of effecting any significant change in the EU's rules on medicines are virtually zero in the foreseeable future. This year will mark the 50th anniversary of the first EU rules on authorization of pharmaceuticals—Directive 65/65/EEC, which set out the basic criteria of quality, safety, and efficacy. The EU is planning a commemoration later in 2015. But a commemoration of how the current set of rules got started is just about all that can be hoped for right now. It may not be another 50 years before there is any fundamental change to those rules—but it is certainly going to be more than 50 months.

The other missing element in the EMA approach is how medicines are going to be paid for in an adaptive pathways scenario. Admittedly, the agency is energetic in signing up HTA bodies to the pilot. But so far it has not yet managed

to get any payers on board. And that really is the elephant in the room in these discussions. Or, perhaps, the elephant that is not in the room, and ought to be. As some industry executives have observed, there is little incentive for industry to speed up its development programs if at the end of the day it cannot get paid any quicker.

New support committee

Some relief may be provided in another EU initiative that is to take shape in the new year. The EU is establishing an expert group to be known as STAMP, derived as a clumsy acronym from its equally clumsy title of safe and timely access of medicines to patients. STAMP will report to the EU pharmaceutical committee—which consists of member states' senior officials for pharmaceuticals, and has broad responsibility for discussing legislation. Some members of this group are anxious to ensure that EMA does not run ahead too far with its pilot—health matters remain, after all, predominantly a national competence in the EU. STAMP has been given the formal mandate to identify ways of making more effective use of the EU's regulatory framework tools so as to "improve safe and timely access and availability of medicines for patients." The committee will explore the views of member states, and review their national experiences and initiatives in this area. Again, there are limitations to what the committee can and will do. It is going to be looking at the scope for flexibility in current provisions for accelerated assessment, conditional authorizations, authorization under exceptional circumstances on the basis of less complete data, or compassionate use and treatment on a "named-patient basis."

STAMP has no mandate to look beyond the current provisions and suggest reform. Also, since it is composed of representatives or nominees of health ministries, the group's members will, in most member states, have little influence over issues of pricing and reimbursement, because few European countries combine the role of health supervision and payment decisions for medicines.

The scene has been set for some vigorous debate in the coming months over how to speed good new medicines to patients by speeding up and adapting current procedures. But because the debate excludes the possibility of legislative change and has only tenuous links to the tougher world of health system economics and drug pricing, the outcome may prove to be more heat than light, or more talk than delivery.

— *Peter O'Donnell*

CLINICAL TECHNOLOGY

The Use of mHealth in Clinical Trials

In early January, Novartis selected Qualcomm Life as a global digital health collaborator for its Trials of The Future program. That program is designed to leverage healthcare technology to improve the experience of clinical trial participants and patients using Novartis products. Qualcomm Life's 2net Platform is the global connectivity platform for collecting and aggregating medical device data during trials, with the goal to improve the convenience and speed of capturing study subject data and test results to ultimately gain more trial efficiencies and connected experiences for participants. Novartis is currently using the 2net Platform in an observational study that is evaluating the use of mobile devices with chronic lung disease patients.

Also in January, Oracle announced the availability of its InForm Medication Adherence Insights Cloud Service, which uses technology acquired from Proteus, an FDA-approved ingestible sensor platform. When combined with clinical trials medication, it can provide rapid validation of the quantity of medication a patient ingests and the time of ingestion of those drugs. It helps identify medication adherence issues early, improving dosage decisions, and enhancing drug safety.

And late last year, Medidata Solutions announced the completion of a method development project conducted with GlaxoSmithKline to evaluate the impact of unifying mHealth devices with cloud-based technologies in a clinical trial setting.

The collaborative project took place at GSK's Human Performance Lab. Program participants were provided with two wearable devices to continuously measure vital signs, electrocardiogram (ECG) data and activity levels. In addition, participants used Medidata Patient Cloud®, a mobile app for patient-reported outcomes and they carried smartphones that captured data from the mHealth devices, which then pulled data into the Medidata Clinical Cloud® and mapped it to clinical records.

The program demonstrated that mHealth technologies have the power to comprehensively collect large volumes of objective data that is reliable, secure and analysis-ready, and provides real-time, continuous insight into the well being of patients. All of the data collected was audited and is compliant with FDA regulations. Additionally, the effort indicated that mobile devices can support the long-term goal.

Medidata intends to use the technology infrastructure developed for this initiative as a model to enable new Phase I–IV mHealth clinical trials, which the company will be supporting for clients over the coming months. More information is available at http://bit.ly/1C7A0Yv.

These developments point to the increased use of mHealth and digital technologies provided by pharmaceutical companies to help improve clinical trials. But what is the uptake in the industry? And is mHealth poised to change the clinical trials landscape?

mHealth survey results

Applied Clinical Trials and SCORR Marketing collaborated on the survey "mHealth Use in Clinical Trials" late last year to answer those questions and identify trends and attitudes among professionals involved in clinical trials.

From FDA involvement, to the definition of mHealth to the benefits and challenges of mHealth, were included on the survey.

Top-line results, such as those presented in Figure 1, show an almost equal use of mHealth in clinical trials as to not using mHealth technologies in trials.

Yet, another survey question showed that the majority of the respondents have been using mHealth technologies in clinical trials for over two years.

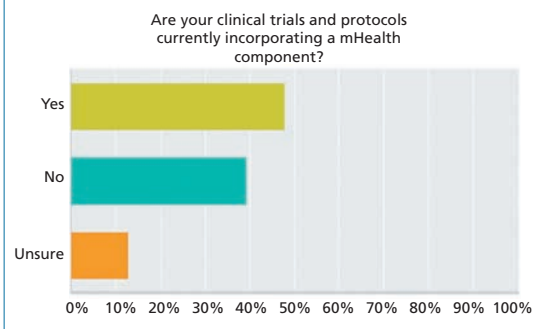
As mHealth or digital health technology availability increases in the healthcare arena, adoption rates and benefits remain unclear. However, in clinical trials, according to our survey, the benefits are clear. Participants believe that mHealth will improve the following in order:

- Data quality in the trial
- Patient trial adherence
- Patient engagement
- Safety and signal detection

Applied Clinical Trials will continue to cover mHealth as it emerges in our industry. SCORR Marketing has created a full report from the survey results, which is available for download at http://bit.ly/1Es4Uc3.

— *Lisa Henderson*

Measuring Mobile Health Impact



Source: *Applied Clinical Trials*, SCORR Marketing

Figure 1. One of the questions asked in *Applied Clinical Trials* and SCORR Marketing's survey on understanding the use of mHealth in clinical trials.

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GLOBAL REPORT

Terrorist Attacks Have No Impact on EuroMeeting, Says DIA

The combined EuroMeeting and Clinical Forum, slated for mid-April, will take place in Paris as planned, in spite of January's terrorist attacks in the French capital, according to the Drug Information Association (DIA).

"We are working closely with the venue and the city of Paris to make sure all security measures are taken and on-site security will be reinforced," says Natacha Scholl, team leader of operations for DIA in Europe, Middle East & Africa. "We will put everything in place to reassure participants, of course."

Scholl does not anticipate that the attacks will have any great impact on delegate numbers. "Registrations haven't stopped over the past days, despite the tragic events," she says.

As of Jan. 15, there were already more than 650 registered participants, and Scholl said the organizers are expecting at least 2,500 to 3,000 attendees in total for the two events. The EuroMeeting and Clinical Forum have never before been held at the same location, but there were around 2,500 participants at the 2013 EuroMeeting in Amsterdam and around 2,200 at the 2014 EuroMeeting in Vienna. The Clinical Forum attracts an average of 400 attendees each year.

Globalization remains a key industry trend and one that will be discussed heavily at both events. The continued significance of global markets was listed as the 10th leading trend in pharmaceuticals, according to DIA's second annual "What Lies Ahead?" report.

"It is important for companies to work in global markets, especially in developing markets like China, pan-Asia, Russia and Eastern Europe, India, and Brazil, Argentina, Venezuela, and other Latin American countries, as this is where the majority of future growth will be," wrote the authors.

Successful companies, they said, conduct early stage analysis and planning to account for varying global factors when selecting countries for expansion, and they also create partnerships to address these needs and to build infrastructure, including training of the workforce.

According to the DIA report, "The topic of global markets is, as one thought leader expressed, 'almost an established fact of life and no longer a trend.'"

— *Philip Ward*

DATA ANALYSIS

Five-Year Disease Prevalence Only One Driver of R&D Investment

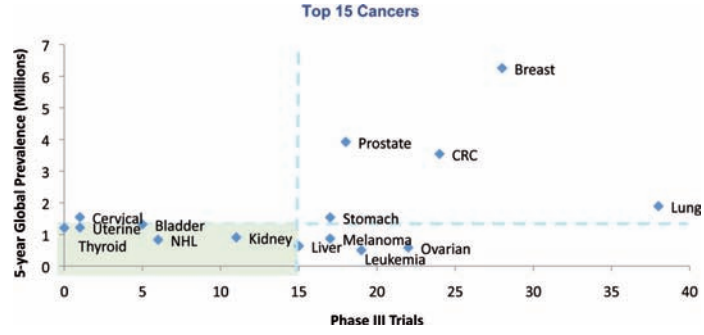
Five-year disease prevalence is certainly a factor—but apparently not the only one—determining which cancer types are most commonly being studied in late-phase clinical trials. IMS Health's analysis of the distribution of Phase III trials reveals that, as would be expected, cancers with higher five-year disease prevalence are the subject of more late-phase trials. But there are exceptions (see Figure 1).

The first is lung cancer. It is the clear leader in terms of the volume of Phase III trials, yet has about the same five-year prevalence as cervical and stomach cancers, both of which are involved in dramatically fewer trials. This may be tied to the fact that the molecular targets in non-small cell lung cancer have been long-since identified and extensively studied. The second exception is ovarian cancer, which has one of the lowest five-year prevalence rates, but is being heavily studied in Phase III trials due to the fact that several genetic mutations can affect the outcome for ovarian cancer patients.

Thus, a low five-year disease prevalence does not always inhibit research investment, provided that the genetic target can be identified in patients.

— IMS *Health*

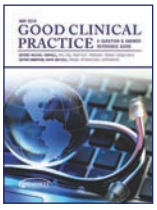
Phase III Trials by Cancer Type and 5-year Disease Prevalence



Source: IMS Health Global Oncology Trend Report

Figure 1. According to WHO, five-year prevalence is "defined as the number of persons in a defined population who have been diagnosed with that type of cancer, and who are still alive at the end of the period."

Essential Publications for **Clinical Research Professionals**



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Closing in on Opportunities to Simplify Protocol Design

New study highlights the importance of focusing on non-core procedures to better optimize study design

Sponsor companies face intense pressure to deliver higher levels of efficiency and drug development performance. A growing number of sponsors are now acting on the belief that improvements in protocol design feasibility hold the key to addressing and easing some of these pressures. Although changing legacy protocol design practices and operating procedures is extremely difficult, sponsor companies are implementing new mechanisms and approaches—beginning with a focus on reducing non-core procedures, protocol amendments, and excessively administered core procedures.

A recent 2014 study by the Tufts Center for the Study of Drug Development (CSDD) provides an update on the prevalence of non-core procedures and sheds new light on their causes. Key takeaways include:

- Sponsors report that a higher percentage of protocol procedures now support supplemental, tertiary, and exploratory endpoints compared to that reported in 2012.
- A closer look at non-core procedures shows that a high percentage is associated with safety and efficacy endpoints.
- Most non-core data is source data verified and included in regulatory submissions.

About the 2014 study

This follow-up study sought to understand more about the purpose of non-core procedures, their characteristics, and how non-core data is used. Eight sponsor companies participated, each providing approximately 15 protocols. In total, 137 unique Phase II and III protocols conducted since 2009 and having at least one procedure tied to a primary endpoint were analyzed. The protocols targeted diseases across multiple therapeutic areas and were executed by investigative sites dispersed globally. To minimize unusual and atypical designs, pediatric, medical device, orphan drug, and extension studies were excluded from the sample. The scope and characteristics of protocols analyzed in this study were generally consistent with industry benchmarks (i.e., number of countries, sites, and patients; total number of procedures and eligibility criteria).

Medidata Solutions not only sponsored the 2012 study but also sponsored this subsequent effort and provided a custom e-solution to collect each company's data and to tie protocol procedures to their direct costs. Participating companies classified a total of 25,287 procedures according to the objective and endpoint that each supported as defined by the clinical study report (CSR) and the study's statistical analysis plan (SAP).

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

The procedure classification scheme used in this study was identical to that used in the original 2012 study:

1. "Core" procedures—are those that support primary and/or secondary study objectives or primary or key secondary and safety endpoints.

2. "Required" procedures—are those that support screening requirements and compliance-related activity, including drug dispensing, informed consent form review, and study drug return.

3. "Standard" procedures—are those that are commonly performed during initial and routine study participant visits, including medical history, height and weight measurement, adverse event assessment, and concomitant medication review.

4. "Non-core" procedures—are those that support supplemental secondary, tertiary, and exploratory endpoints, and safety and efficacy procedures not associated with a study endpoint or objective.

Characterizing non-core procedures

Nearly one-third of all Phase III protocol procedures (30.6%) supported non-core endpoints and objectives, up from 24.7% observed in the earlier study. Nearly one in five Phase II procedures (20.7%) supported non-core endpoints and objectives, approximately three percentage points higher than the 2012 study level. The proportion of procedures supporting core endpoints also increased: from 54.3% to 64.9% of Phase II procedures, and from 47.9% to 58.6% of Phase III procedures. In the later study, a smaller relative proportion of Phase II and Phase III procedures were classified as standard and required. Similar to the 2012 study, variability across therapeutic areas was observed, with protocols targeting endocrine and central nervous system (CNS) disorders

having the highest incidence of non-core procedures.

Procedures supporting non-core endpoints were evenly distributed across the entire schedule of assessments. Twenty-two percent and 32.6% of all non-core procedures in Phase II and III studies, respectively, supported safety endpoints. And 13.7% and 21.6% of all non-core procedures in Phase II and III trials supported efficacy endpoints. Less than 20% of all procedures that collected non-core data supported outcomes-related endpoints, such as quality of life assessments and reimbursement. Only 3% of non-core procedures collected biomarker data supporting regulatory filings.

Costs of collecting non-core data

The proportion of each study budget supporting the direct cost of administering non-core procedures also increased. Approximately one-quarter (23%) of each Phase II and III study budget covered the direct cost of administering non-core procedures. This proportion is up from an estimated 18% in the 2012 study.

The direct cost proportion of the study budget is only part of the total cost picture. The in-direct costs (e.g., the cost of collecting, monitoring, cleaning, analyzing, managing, and storing non-core procedure data) must also be considered. Although organizations have difficulty measuring fully loaded in-direct costs accurately, participating companies looked at a number of factors to begin characterizing these in-direct costs.

This recent Tufts CSDD study found that 80% of all data from Phase II non-core procedures and 87% of all data from Phase III non-core procedures was source data verified by study monitors. And although non-core data does not support primary or key secondary endpoints, participating sponsor companies reported that nearly all of their non-core data was included in the clinical study report (92%) and in the tables, listings, and figures (95%) in the regulatory submission.

Simplification steps

Non-core procedures are added to protocols for a variety of reasons: Clinical teams and statisticians often want to collect more contextual data to help interpret study findings and guide development decisions. These context-setting variables provide clinical validation and explanation for unusual and unexpected results that may be observed during a clinical trial. Clinical teams also collect additional study data hoping that, should the study fail to meet its original objectives, post-hoc analyses might reveal useful new insights into the characteristics and treatment of disease. Most companies can point to exploratory data that led to the discovery of a novel therapy.

But a growing number of sponsor companies now admit that the presence of non-core protocol procedures may also be due to habit and risk-avoidance. Professionals involved with protocol authoring may permit outdated and unnecessary procedures into new protocols because they are routinely included and copied from old authoring templates and policies. And clinical teams are collecting additional data in cautious anticipation of requests from regulatory agencies, health authorities, purchasers, and payers.

The higher reported percentage of protocol procedures now supporting supplemental, tertiary, and exploratory endpoints compared to that reported in 2012 is a curious finding. Sponsor companies may be continuing to add more non-core procedures to their study designs. The higher reported proportion may also be due to greater awareness and more aggressive identification of non-core procedures as a growing number of companies look for ways to simplify their protocol designs and improve study feasibility.

Indeed, a separate 2014 Tufts CSDD study found that a number of companies are using new protocol authoring techniques that include more robust evaluations (e.g., SPIRIT authoring checklist and the Metrics Champion Consortium Protocol Quality Scoring Tool) to better tie procedures to core endpoints and objectives.

Most major and mid-sized pharmaceutical and biotechnology companies are now taking formal steps to routinely examine the operational feasibility of their study designs. Many organizations have established feasibility review committees to challenge non-core and excessively conducted core procedures. Reports to date on the effectiveness and impact of these committees are very positive: 93% of companies report that their feasibility review committees are "somewhat" or "very" effective. And a high percentage of companies with established committees report that they have seen fewer protocol amendments (68%); a reduction in investigative site burden to administer the protocol (53%); and faster study cycle times (44%).

Non-core procedures represent an important area of initial focus for companies seeking opportunities to optimize study design. Non-core procedures should be more carefully scrutinized and the trade-off between their benefits and cost assessed. As part of that assessment, sponsors and CROs can determine whether to delay or remove non-core procedures if the cost of doing so outweighs their benefit. The recent Tufts CSDD study provides further insight into the purposes of, and practices associated with, procedures supporting non-core endpoints and objectives. The marginal cost of including a single non-core procedure may be very small relative to the overall total study budget. But in the aggregate, non-core procedures consume up to a third of the total direct procedure cost in a Phase III study budget, and many magnitudes more in in-direct study costs.

Integrated Clinical Research Systems: A Chance to Reinvent

Richard G. Pellegrino MD, PhD

Adoption of model could shorten development time and boost efficiency for market-pressured sites.

The organization of healthcare is changing rapidly. The healthcare delivery system is increasingly powered by payers and regulators, and this directs both clinical medicine and drug development. Partly because of this change, the drug development process has been heavily scrutinized, and a great emphasis has been placed on more efficient translation of basic science into useful medicines. In response, the pharmaceutical and healthcare delivery industries (hospitals and outpatient physician services), the two largest players in the post-clinical translational medicine process, are spending billions of dollars to make major changes in the way they operate. These changes, made at the expense of these two industries, present a unique opportunity to reinvent the clinical trial site industry.

Challenges drive consolidation

The changing healthcare marketplace has caused healthcare providers to consolidate.[1] Hospitals have either closed or organized themselves into ever larger systems, trying to capture greater market share and utilize economies of scale in order to best respond to falling reimbursements. Physicians have not been immune. The number of employed physicians has risen 34% from 2000 to 2012 as hospitals and physicians merge into integrated healthcare systems around the country.[2] Approximately 60% of hospitals now utilize hospitalists, and they are rapidly replacing independent hospital staff.[2] The advent of metric-based payment schedules and accountable care organizations have demanded that hospitals have more control and a better understanding of how care is conducted within their walls and in clinics. In response, billions of dollars have been spent on electronic medical record (EMR) systems that create searchable databases of unprecedented size and detail. These databases cover both the inpatient and outpatient activities of these growing integrated systems. The emphasis on up-to-date problem lists and the adoption of ICD-10 billing codes has made diagnostic documentation more precise.

The pharmaceutical industry has followed suit, driven by falling reimbursements and the growth of the generic drug industry.[3] They have undergone massive consolidation, long ago shedding much of their drug development operations to contract research organizations (CROs). Early R&D is increasingly becoming the responsibility of biotechnology companies, as evidenced by Merck & Co.'s recent layoff of thousands of employees, mostly from R&D. In addition, conversion of clinical trial data capture from paper to electronic systems is just about complete.

All this activity is an attempt to adapt to the changing marketplace. In response to falling prices and rising generic competition, companies need to reduce costs to continue to sell in "commoditized" markets, such as hypertension. In addition, they need to find new markets with less competition and, hopefully, better margins (i.e., diseases without adequate treatment). Both of

these strategies put pressure, albeit different types of pressure, on the drug development process.

New pressures on sites

In the pharmaceutical industry, reduction in development costs should mean shorter development times. However, clinical development timelines continues to rise. From 2000-2012, mean clinical development time has risen from 6.3 years to 6.8 years, even as the mean time to regulatory approval has been halved.[4,5]

Why? Because successful drug development plans now require a greater number of studies before approval than they did 14 years ago. Moreover, these studies are more complex, demanding larger pre-screen patient pools and more efficient recruitment techniques. Most new drugs, particularly those with the greatest humanitarian and economic potential, are difficult in this regard. Many orphan drugs, by definition, look at more obscure patient populations. Genomic drugs also look at greatly narrowed patient populations and require more precise data on each individual. Even more common, devastating diseases for which there is no treatment, such as Alzheimer's disease, demand more complex approaches, as simpler approaches prove to be inadequate. In all these cases, the major rate-limiting step is slow recruitment.[6,7,8] The message is clear. Sites must find a way to draw from larger patient populations in a more systematized and precise way.

It won't be easy. In spite of these pressures, the clinical trials site system, designed in another era, continues to operate as a cottage industry. By definition, cottage industries lack the cohesiveness and resources necessary for sustained coordinated change. The most basic unit of clinical trial execution, where the protocol meets the subject, continues to be the individually owned clinical research site. The best of these sites are led by competent professional clinician investigators, but their patient bases and financial resources are limited.

Working within this system, the pharmaceutical industry has responded by increasing the number of sites per study; if 30 doesn't do it, maybe 200 will. This Band-Aid approach involves bringing in many novice investigators and often stretches the ability of pharmaceutical companies and regulators to ensure quality. Further, it has not resulted in a shortened clinical development time. With the entire drug development process taking an average of 15 years on a 20-year patent, time is of the essence.[9]

A more efficient clinical trial unit

What is needed is a more efficient clinical trial unit, with greater resources, true inpatient, outpatient, and multispecialty capability, more capital, and a much larger patient base connected by an EMR system operating in real time. But how does this transition take place in such a fragmented industry? The National Institutes of Health (NIH) thinks it has the answer for NIH-sponsored research.[10] In December 2011, the NIH created its 27th Institute, the National Center for Advancing Translational Sciences (NCATS). NCATS has adopted the institutional Clinical and Translational Science Award (CTSA) program that was initiated by the NIH in 2006. Under NCATS, the goal of the CTSA program remains focused on integrated "academic homes" for the clinical and translational sciences that increase the quality, safety, efficiency, and speed of clinical and translational research, particularly for NIH-supported research.

Institutional CTSAs are made to degree-granting institutions or groups of institutions that receive significant funding from the NIH. CTSAs require:

- Institutional commitment
- The effort achieves "the status of a major scientific and administrative entity within and across an applicant and partner institution(s)"
- "API(s) with the authority and influence necessary to successfully create an institutional home for clinical and translational research"

In other words, the effort should be taken seriously by the institution and should be piloted by a strong leader who has the authority to gather and direct the resources needed to get the job done. This is a tall order for a research enterprise that, by definition, has to operate across many departments and existing programs in a highly decentralized academic environment.

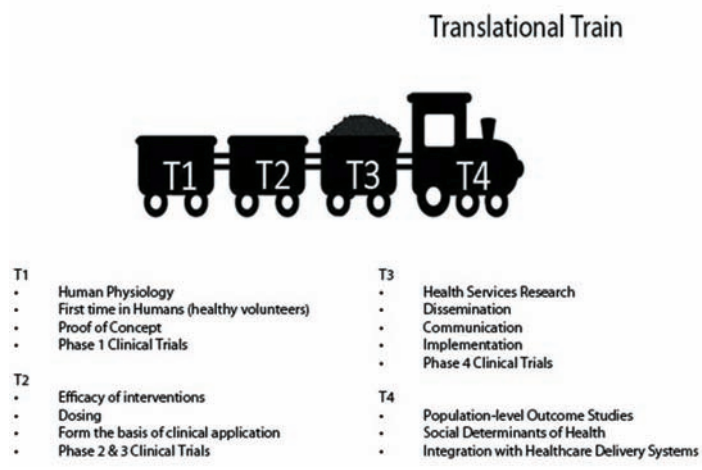
In spite of the difficulties of implementing this concept in academic institutions, the NIH has a few things going for it. It has the resources and, therefore, the influence to support a change in the way academic clinical research is done. In contrast, the fragmented clinical trial site industry has no such rich uncle. If the answer for the NIH is the concept of "academic homes," how would that translate into the private sector? Who will provide the capital and the drive?

How will this transition occur?

We need to take a look at the process of translational medicine. Figure 1 (see page 22) illustrates the journey of a molecule from "first time in man" to a fully utilized member of the pharmacopeia. Molecules enter at T1, and 5% of them emerge, about 15 years later, at T4, as safe and effective drugs that are integrated into healthcare delivery systems.

A major rate-limiting step involves the planning and execution of clinical trials in T1 and T2. This job is done cooperatively between the pharmaceutical and clinical trial site industry. On the face of the matter, it may seem reasonable for the pharmaceutical industry to eliminate this step by using its formidable resources to buy sites and make them into more efficient entities.

Translational Medicine: A Journey With Many Stops



Source: Pellegrino

Figure 1. The journey of a molecule from human studies to a fully functional member of the pharmacopeia.

This cannot happen, since by design, these two players must remain under separate ownership to ensure objectivity. Clinical sites—an independent contractor participating mostly in multisite studies and blinded to the drug—would have difficultly willfully influencing the outcome of a trial if they wanted to. The compensation structure, where sites are paid for work done regardless of the outcome of the trial, removes the motive to do so.

If the clinical trial site industry cannot look to pharma for the capital necessary to create a more efficient system, where can they go? They must look to the healthcare delivery industry. More specifically, competent professional clinician investigators must merge with integrated medical systems to form integrated clinical research systems. For the site wishing to integrate into the larger system, costs vs. starting a standalone site are not the issue. The key is cooperation with the system, and time and perseverance to integrate with their existing procedures and assets. However, if additional capital is needed, it can come from the medical systems, which will see the business sense of reorganizing their existing assets to provide a new service.

The integrated clinical research system

Integrated clinical research systems could take many forms, but are essentially research arms of large integrated medical systems, run by an experienced investigator, that has access to the larger institution's EMR and clinical resources. Installing the integrated clinical research system as the new basic unit of clinical research creates a single business unit for the entire translational process. Some of its advantages are as follows:

Broader patient base with real-time access: Integrated medical systems tie together hundreds of thousands of inpatients and outpatients in real time with EMR. The scale of the database is orders of magnitude greater than what could be constructed by a standalone site. Although size and complexity have their own problems, the power of a large integrated entity, with the necessary resources to provide data, in real time, with large number of search fields and the availability of 24-hour IT support is very different from what the standalone site could provide.

Better feasibility assessments: To better understand the power of integrated clinical research systems to develop improved development plans and protocols, let's examine the "translational train" in Figure 1 again. There are a few things to notice:

- It is difficult and risky to go from car to car as evidenced by the high failure rate and long development times
- The train is powered by T3, but is run by T4
- Most importantly, trains are pulled

We most often think of drugs as being pushed through the drug development process, but, in fact, in the new healthcare delivery system they are more often pulled through by the payers. If there is no market for the drug in T4, then there is no sense in proceeding. Pharmaceuticals must be integrated into the changing healthcare delivery system. It is obvious that sponsors understand this, as evidenced by the adoption of "payerspeak" in many new protocols, with numerous studies having endpoints like "reduction in hospital length of stay" or "readmission rates."

Integrated clinical research systems will contain expertise across the entire spectrum of the post-clinical translational process, including knowledge of current payment systems. They can form teams that not only include clinical personnel, but everyone involved in T3 and T4, all of whom are represented in the integrated medical system. Teams consisting of physicians from all specialties, pharmacy managers, insurance company personnel, database managers, case coordination, billing, and administration can evaluate development plans on the front end, commenting on their eventual suitability for T3 and T4.

In addition, integrated clinical research systems are well positioned to advise on the feasibility of individual protocols. Instead of opinion, the percentage of potentially eligible individuals could be determined precisely, using sample sizes in the hundreds of thousands in real-world situations. This will

reduce the number of costly and time-consuming protocol amendments[11,12,13] and will result in better protocols, reducing the failure rate and accelerating the drug development process, particularly in T1 and T2.

Safer Phase I units: Pressure to reduce the utilization of inpatient beds have produced a surplus. Integrated clinical research systems have the capacity to place Phase I units within hospitals. This gives them access to immediate consults from all specialties, as well as the rapid response and code teams.

> **Entire development plans can be made more coherent by utilizing accurate real-time information from a variety of sources at the end of the translational pathway.**

Increased access to capital and resources: Integrated clinical research systems have complete compliance and marketing departments, as well as fully staffed pharmacies. The system owns all diagnostic equipment necessary to run a hospital and clinic and generally employs or has relationships with doctors in every specialty.

The formation of full-scale integrated clinical research systems will be difficult and will take time. However, widespread adoption of this system will go a long way toward shortening development times by improving the design and implementation of individual protocols. More importantly, entire development plans can be made more coherent by utilizing accurate real-time information from a variety of sources at the end of the translational pathway, hopefully resulting in more and better drugs to treat the devastating diseases that afflict our patients.

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Key Strategies in Sustaining the Investigator Pool

Elisa Cascade, Claire Sears, PhD, Mark Nixon, PhD

Understanding the operational burden for sites and implementing valuable supportive solutions.

The sharp rise in ongoing clinical research studies is driving demand for greater participation in research by physicians as well as by patients.[1] However, numbers of principal investigators filing the Food and Drug Administration (FDA) Form 1572 fell globally from 27,861 in 2008 to 23,935 in 2009 and 22,243 in 2010.[2] In addition, within the pool of investigators who have filed a 1572, turnover rates are high, with 35% of investigators in the U.S. not returning to conduct another clinical trial by 2014 since initially submitting a 1572 in 2006.[3] The corresponding figures are even higher outside of the U.S.: 55% for Canada, 53% for South America, 53% for Asia Pacific, and 47% for Africa (see Figure 1 on facing page).[3] The impact of this high investigator turnover in industry-sponsored clinical trials is significant, contributing to escalating costs for site selection, qualification, training, and start-up.

In parallel to pursuing strategies for attracting and training new investigators to clinical research, it is also vital to obtain a better understanding of why investigators stop doing research after only one clinical trial, and to explore options for addressing these issues. A review of the literature suggests that barriers may be system or organization-related as well as trial and physician-related.[1,4,5] System and organization-related barriers include time involvement (e.g., research-related work, discussions with patients, grant applications, and ethics submissions) and resource issues (e.g., costs involved in research participation, facilities and infrastructure, and requirements of sponsors).[1] Trial-related barriers include lack of clinical or scientific rationale for the research, increasing complexity of trials, excessive trial costs not covered by the trial sponsor, and inferior trial medications compared to standard therapy. Physician-related barriers include lack of interest in the research topic, limited familiarity with research procedures, lack of allied support staff, and disruption to clinical practice.

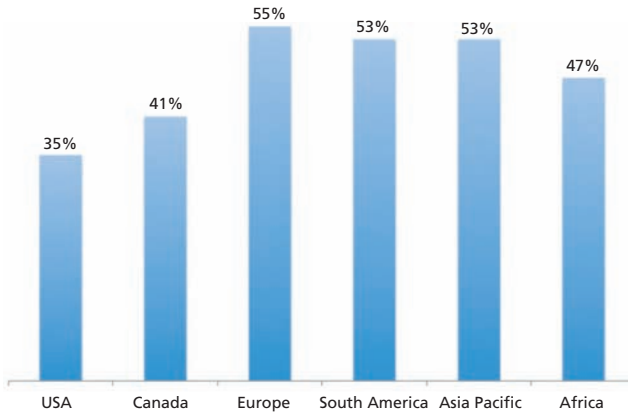
While some of these barriers are immovable (e.g., ethics submissions), many of the system, organization, and physician-related barriers are under the control of the research sponsor and its contract research organization (CRO) partners. In order to help the industry identify solutions to decrease the high investigator turnover rates, we conducted a global survey to solicit actionable feedback from investigators on the burden associated with participating in clinical trials.

Methods: Global survey of 750 investigators

To better understand the burden placed on investigators by clinical operations and the potential value of supporting solutions, DrugDev surveyed 750 clinical trial investigators from its Global Network in seven countries (Argentina, Australia, Germany, India, South Africa, the U.K., and the U.S.). An invitation to participate in the 25-question online survey was emailed to approximately 11,000 randomly selected investigators. The survey was open from Oct. 28 to Dec. 3, 2013. Respondents were offered the chance to win one of five iPads.

Respondents rated the questions on investigator burden and supporting solution value on a five-point Likert scale: extremely burdensome/valuable; very burdensome/valuable; somewhat burdensome/valuable; a little burdensome/valuable; and not at all burdensome/valuable. Questions were scored based

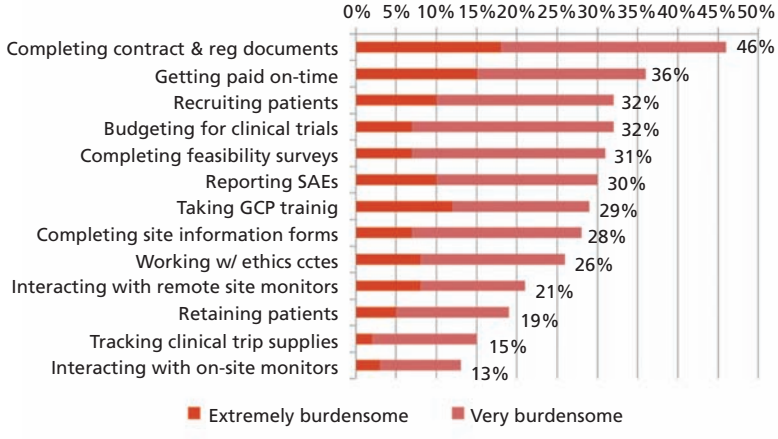
Investigator Turnover by Region



Source: CenterWatch 2011

Figure 1. Investigators who have not returned to conduct another clinical trial since initially submitting a 1572 in 2006.

Investigator Burden



Source: Cascade et al.

Figure 2. The level of burden associated with clinical trial operations.

on the sum of the top two categories: extremely and very burdensome/valuable.

We examined the data for variation by country of origin using the Cochran Mantel-Haenszel statistic for categorical ordinal variables. The U.S. was used as the reference country. In addition, we looked for variation based on previous research experience as measured by the investigator-reported number of previous studies (two or fewer studies, three to 10 studies, and more than 10 studies), also using the Cochran Mantel-Haenszel statistic, with investigators who had conducted more than 10 studies as the reference group.

Results: Sample characteristics

The target sample for this group was 750 completed responses, weighted to the U.S. to reflect global investigator distribution.[3] Emails were sent out to achieve the sample size, and as soon as these targets were achieved the survey was closed. Anyone responding after that time was not included in the analysis. A total of 750 investigators responded, with nearly half (45.9%) of the total responses coming from the U.S. An overall response rate of 7% was achieved (750/11,000), ranging from a low of 4% for Germany to a high of 14% for Argentina (see Table 1 on page 26).

As seen in Table 1, 8.1% of respondents reported that they had participated in two or fewer trials, 37.7% participated in three to 10 trials, and 54.1% participated in more than 10 trials. Most reported having experience in more than one therapy area (an average of 3.5 per investigator), including cardiovascular (26.8%), internal medicine (25.3%), endocrinology/diabetes (24.9%), and pulmonary/respiratory (20.9%).

Results: Investigator-reported burden

As shown in Figure 2, completing contractual and regulatory documents was the most burdensome administrative activity for investigators (46% rated this as very or extremely burdensome), with getting paid on time rated as the second most burdensome issue (36% found this issue very or extremely burdensome). Other factors identified as very or extremely burdensome included recruiting patients (32%), budgeting for clinical trials (32%), completing feasibility surveys (31%), and reporting serious adverse events (SAEs, 30%).

Table 2 (see page 27) summarizes differences seen at the country level and by experience level. There was significant variation by country in six of the factors, with the largest differences seen between investigators in Argentina and the U.S.: reporting SAEs, completing site information forms, working with ethics committees, interacting with remote site monitors, and tracking clinical trial supplies. With the exception of patient recruitment, investigators in other countries rated these factors as being more burdensome than those based in the U.S. For patient

Sample Characteristics		
VARIABLE	**#(N=750)**	**%**
Country-level response rates:*		
• **Argentina**	93	14.5%
• **Australia**	61	7.7%
• **Germany**	60	4.0%
• **India**	81	8.5%
• **South Africa**	45	10.1%
• **United Kingdom**	66	7.0%
• **United States**	344	5.6%
Experience:		
• **0 to 2 studies**	61	8.1%
• **3 to 10 studies**	283	37.7%
• **>10 studies**	406	54.1%
Average therapeutic areas per investigator	3.5	-
Therapy areas with 100+ mentions:		
• **Cardiovascular**	201	26.8%
• **internal Medicine**	190	25.3%
• **Endocrinology/Diabetes**	187	24.9%
• **Pulmonary/Respiratory**	157	20.9%
• **Gastrointestinal**	124	16.5%
• **Primary Care**	121	16.1%
• **Infectious Disease**	117	15.6%
• **Vaccines**	111	14.8%
• **Neurology**	109	14.5%
• **Rheumatology**	107	14.3%
• **Dermatology**	106	14.1%
• **Musculoskeletal**	106	14.1%

*Calculated based on: responses received/total emails sent to investigators in that country.

Source: Cascade et al.

Table 1. Investigator characteristics by country, experience, and therapeutic area.

recruitment, however, significantly fewer investigators in Argentina (p=0.0008) and India (p=0.0011) found this activity to be extremely burdensome.

With respect to clinical trial experience, seven items were significantly more burdensome for less experienced investigators who had completed two or fewer studies as compared to the most experienced with more than 10 studies: completing contracts and regulatory documents; budgeting for clinical trials; working with ethics committees; interacting with remote site monitors; retaining patients; tracking clinical supplies; and interacting with on-site monitors. Retaining patients in the study was also significantly more burdensome for investigators with three to 10 studies when compared to the group with more than 10 studies.

In contrast, one item, getting paid on time, was rated as more burdensome by experienced investigators, with 44% of those who had completed more than 10 studies finding this extremely or very burdensome, compared with only 16% of those who had completed zero to two studies.

Results: Value of supportive solutions

When asked what support functions would be helpful, more than 70% of global investigators indicated that the following five approaches would be extremely or very valuable (see Figure 3 on page 28):

1. Completing good clinical practice (GCP) training once every two years only, and uploading the training certificate to a central website accessible to multiple study sponsors (85%)

2. Uploading CVs to a central website accessible by multiple sponsors, reducing document collection on study start-up (79%)

3. Guaranteed investigator payment within 30 days (78%)

4. Annual Master Service Agreement (MSA) with cross-pharma repository of essential documents (75%)

5. Cross-sponsor sharing of contractual preferences (73%)

Table 3 (see page 29) shows that there are two primary areas of variation at the country level: patient recruitment and patient retention. Both of these were rated as less valuable among respondents in several countries when compared to those in the U.S. In addition, access to contract clinical trial support staff was viewed as being significantly more valuable in Argentina, Australia, India, and the U.K.

The value of activities associated with clinical trial support also showed some variability based on the level of investigator experience (Table 3). In particular, there was a statistically significant difference between investigators who had carried out zero to two studies compared to those with 10 studies for the response of guaranteed payment within 30 days. Investigators with zero to two clinical studies placed less value on this factor, with 67% of investigators rating this very or extremely valuable, compared to 83% of investigators who have completed more than 10 studies.

In addition to guaranteed payment within 30 days, more experienced investigators (both three to 10 and more than 10 studies) also rated the ability to upload their CV to a cross-sponsor website as significantly more valuable than less experienced investigators. In contrast, access to contract clinical trial support staff was rated as more valuable by investigators with fewer than two and three to 10 studies. Provision of patient retention emails/texts was rated as more important by investigators with three to 10 studies as compared to zero to two or more than 10 trials.

Limitations

Although these findings have important implications for how to decrease the burden of clinical trial operations, the study does have some limitations. First, the study was conducted among a sample of investigators who are members of the DrugDev Network, and it is possible that the characteristics of the population could have influenced the results. For example, enrollment in DrugDev may self-select for investigators who are more comfortable accessing and sharing information online. However, given that online and mobile communications are standard practice today (86% of clini-

Investigator Burden Variations			
FACTOR	**COUNTRY P-VALUE**	**EXPERIENCE P-VALUE**	**FINDINGS**
Completing contract & regulatory documents	0.2519	0.0010	More burdensome for investigators with 2 or fewer studies
Getting paid on time	0.9414	<0.0001	Most burdensome for investigators with > 10 studies
Recruiting patients	0.0056	0.1332	Less burdensome in Argentina and India
Budgeting for clinical trials	0.5218	0.0196	More burdensome for investigators with 2 or fewer studies
Completing feasibility surveys	0.9203	0.1505	No significant differences
Reporting SAEs	0.0060	0.1072	More burdensome in Argentina and Germany
Taking GCP training	0.6091	0.7130	No significant differences
Completing site information forms	0.0041	0.0850	More burdensome in Argentina, South Africa, and UK
Working with ethics committees	<0.0001	0.0080	More burdensome in Argentina, Australia, and UK. More burdensome for investigators with 2 or fewer studies
Interacting with remote site monitors	0.0013	0.0016	More burdensome in Argentina. More burdensome for investigators with 2 or fewer studies
Retaining patients	0.2774	<0.0001	More burdensome for investigators with 2 or fewer studies and 3 to 10 studies
Tracking clinical trial supplies	<0.0001	0.0165	More burdensome in Argentina. More burdensome for investigators with 2 or fewer studies
Interacting with on-site monitors	0.5316	0.0499	More burdensome for investigators with 2 or fewer studies

Source: Cascade et al.

Table 2. Variation in investigator burden ratings by country and experience.

cians now report use of smartphones in their professional activities[6]), it is unlikely that this had a significant impact on results.

While the response rate seen in this survey was similar to those reported for online surveys in other publications,[7] another limitation of the study design is the potential for non-response bias. Despite the fact that the proportion of non-responders was high in this study, the results are consistent with comments made by industry experts who have suggested study start-up and ethics as large sources of burden for investigators as well as a trend toward higher protocol complexity posing challenges to patient recruitment.

An additional limitation to this survey is that the investigators could only answer the questions put in front of them, and, therefore, were commenting on the burdens and solutions presented as options. To address this limitation, we also included open-ended questions in both the burden and solution section of the survey to try to identify issues that were not highlighted in the survey. Post-survey analyses of these open-ended questions did not identify any additional factors that were consistently raised by investigators.

Finally, while there was no significant difference in level of experience of investigators across all countries, there were differences between the U.S. and Argentina and India. In both cases, the U.S. had a greater proportion of investigators with more than 10 studies (58% for the U.S. as compared to 40% in Argentina and 37% in India), driven primarily by differences in the three to 10 vs. more than 10 study groups.

Discussion

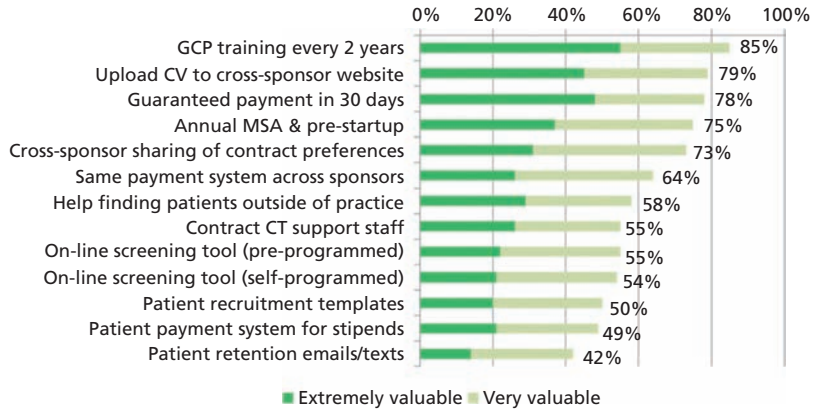
According to analyses conducted by CenterWatch, the Tufts Center for the Study of Drug Development (CSDD), and others using FDA 1572 data, the investigator landscape has shifted in ways that challenge successful conduct of clinical trials (e.g., lower proportion of experienced sites; high turnover among new PIs). The resulting impact for sponsors is higher operational costs, especially related to site identification, qualification, and start-up.

The purpose of this investigator survey was to better understand sources of investigator burden in clinical trial operations and to determine the value to investigators of potentially supportive solutions. Although the literature on investigator burden in clinical trials is limited, our findings appear to be consistent with expert comments.

As described above, completing contractual and regulatory documents was the most burdensome administrative activity for investigators, followed by getting paid on time. The level of burden for these two top-rated factors did not show significant variation at the country level. We did observe some variation in level of burden at the country level across six of the 13 factors tested, especially in Argentina. In general, nearly all of the differences were in system/organization-related factors and five of the six were rated as more burdensome outside of the U.S.

The one area of exception was patient recruitment, which was rated as significantly less burdensome in Argentina and India as compared to the U.S. We hypothesize that this finding may be related to differences in physician/patient relationships and access

Value of Supporting Solutions



Source: Cascade et al.

Figure 3. Support-function approaches that global investigators find would be extremely or very valuable.

to medical care between countries. In Argentina, for example, the large concentration of population in the cities combined with a low rate of mobility encourages close relationships between patients and investigators, who can quickly identify appropriate patients from their practice and encourage them to learn more about clinical trials[8] The low barrier related to recruitment in India, however, may be more related to access, whereby patients enrolled in clinical trials are able to access free medical care, tests, and drugs, which they could potentially not afford otherwise.

As one might predict, there was a higher perceived level of burden for a number of activities reported by less experienced investigators compared to more experienced investigators, with seven of the 13 factors being reported as more burdensome by those having done zero to two studies compared to more than 10 studies. Again, the majority of these were system/organization-related factors, where institutions, sponsors, or CROs could provide more support and resources to those early in their clinical research careers. An example of an area where provision of additional support to less experienced investigators could have a significant impact on start-up time, recruitment metrics, and ultimately investigator turnover is completion of contracts and regulatory documents.

Interestingly, getting paid on time was more burdensome to the most experienced investigators, compared to their less experienced colleagues. This, we believe, reflects the fact that investigators in the more than 10 studies category are more likely to rely on the revenue stream gained from payment from industry-sponsored studies for their business.

Understanding the feedback on sources of burden, it is not surprising that the supportive activities that offered the most value to investigators were items that either guaranteed payment, or streamlined start-up such as GCP training, contracting, and essential document collection. Although there is no benchmark with which to compare, the level of value assigned to these activities was high in absolute terms (rated by more than 70% of the sample as extremely or very valuable).

Although this survey is among the first to quantitatively document the value of solutions to reduce investigator burden, including variation by country and level of experience, the findings are consistent with the opinion of industry experts.

Recognizing that system/organizational factors may be outside of the control of the research sponsor, several individual companies and industry organizations have begun to implement solutions to address trial-related sources of investigator burden. For example, TransCelerate BioPharma Inc., a non-profit organization of around 20 biopharmaceutical companies aimed at implementing innovation in clinical research, has created standards for minimum requirements for GCP training, CVs, and site qualification forms amongst other items.[9] In addition, organizations such as the Investigator Databank—a global collaboration between Janssen, Eli Lilly, Merck & Co., Pfizer, and Novartis—have launched online profiles where investigators can post non-protocol-specific documents (e.g., CVs, GCP training certificates, site qualification forms) just once and have them accessed by all participating sponsors.[10] A global network of research sites is also being established by the Alliance for Clinical Research Excellence and Safety (ACRES), with the aim of connecting research sites worldwide through a shared technology platform.[11] The Global Health Network provides a number of different resources to support clinical trial conduct, including a Site Finder network, mostly centered on sites in Africa, Asia, and Latin America. The Society for Clinical Research Sites (SCRS) is a trade association established to represent global clinical research sites, and to support site sustainability.

In addition, a number of organizations are working to improve investigator training and accreditation, among them the Harvard Multi-Regional Clinical Trials Center (MCRT), the Association of Clinical Research Professionals (ACRP), and ACRES.

Moving beyond these initiatives for setting standards and sharing documents, additional opportunities for mutual benefit exist through standardizing confidential disclosure agreements (CDAs) and clinical trial agreement (CTA) clauses where possible; sharing of contractual preferences at the institutional level; and guaranteeing payment within 30 days.

Ultimately, if we are to reverse the trends of declining physician participation and high turnover in industry-sponsored clinical research, pharmaceutical company research sponsors (and

Value-Rating Variation			
FACTOR	**COUNTRY P-VALUE**	**EXPERIENCE P-VALUE**	**FINDINGS**
GCP training every 2 years	0.5513	0.1515	No significant differences
Upload CV to cross-sponsor website	0.3324	0.0173	Less valuable for investigators with 2 or fewer studies
Guaranteed payment in 30 days	0.0611	<0.0001	Most valuable for investigators with > 10 studies
Annual MSA & pre-startup	0.7992	0.4274	No significant differences
Cross-sponsor sharing of contract preferences	0.8288	0.4925	No significant differences
Same payment system across sponsors	0.5444	0.0677	No significant differences
Help finding patients outside of practice	0.0160	0.5277	Less valuable in Argentina, Australia, and UK
Contract clinical trial support staff	<0.0001	0.0005	More valuable in Argentina, Australia, India, and UK. More valuable for investigators with 2 or fewer studies and 3 to 10 studies
Online screening tool (pre-programmed)	0.7220	0.0689	No significant differences
Online screening tool (self-programmed)	0.2739	0.0564	No significant differences
Patient recruitment templates	0.0109	0.3244	Less valuable in Australia and Germany
Patient payment system for stipends	0.1512	0.3666	No significant differences
Patient retention emails/texts	0.0020	0.0313	Less valuable in Argentina, Australia, Germany, & South Africa. More valuable for investigators with 3 to 10 studies

Source: Cascade et al.

Table 3. Variation in investigator value ratings by country and experience.

their CRO partners) must be willing and able to change their processes to decrease the burden for clinical trial investigators.

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The Remote Patient-Centered Approach in Clinical Research

Deborah Covington, Kristin Veley

Examining the design, implementation, and challenges of this direct-to-patient study model.

In the healthcare arena, the concept of patient-centeredness has expanded over the last 50 years, beginning as a term to describe patient engagement in self-health management and evolving to include various aspects of patient engagement in healthcare research.[1] The creation of the Patient-Centered Outcomes Research Institute (PCORI) further solidified the concept of patient-centered research by its dedication to improving healthcare and outcomes by producing evidence-based data for research guided by patients, their caregivers, and healthcare providers.[2]

In this article, the authors discuss patient-centered research (also termed "direct-to-patient") that uses the "remote" study approach. This type of remote patient-centered study puts individuals, rather than investigative sites, at the center of the research process. Both the design and operation of remote patient-centered studies revolve around patients (see Figure 1 on facing page). Remote patient recruitment, enrollment, and retention programs, data collection, and long-term follow-up evaluation offer opportunities to increase research efficiencies. At the same time, this operational approach intensifies patient-centeredness by engaging patients directly in research functions, overcoming geographic obstacles to connect stakeholders, and incorporating patient input into the research process. The remote patient-centered model offers great potential to advance both observational studies and randomized controlled clinical trials.

Remote, patient-centered research has been conducted in observational studies for more than two decades, most commonly in the form of registries. These non-interventional studies typically follow patients with a particular disease or exposure longitudinally to examine the occurrence of associated health outcomes. For example, pregnancy registries monitor women and their offspring who were exposed to certain medications during pregnancy to observe possible adverse outcomes, such as birth defects.[3]

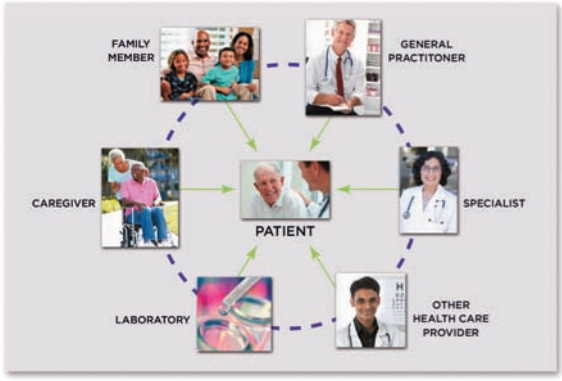
More recently, drug developers have been exploring potential applications in interventional clinical trials. Forerunners such as the REMOTE (Research on Electronic Monitoring of OAB Treatment Experience) pilot trial sponsored by Pfizer (see page 32) have sparked increasing applications of remote patient-centered study designs in efforts to increase access to patient populations and to improve operational efficiencies.[4,5] Although this methodology is still in early stages of development, interest and support from regulators, sponsors, and patients likely will propel it forward in the near future.[6,7]

The purpose of this article is to examine the remote patient-centered study approach in clinical research. First, we review design and operational elements of remote patient-centered studies. Next, we address some of the challenges to conducting remote patient-centered studies. Finally, we discuss the types of studies best suited to the remote patient-centered study approach.

The remote patient-centered study approach

Most remote patient-centered studies share three basic characteristics: patient engagement; use of

All About the Patient



Source: Covington et al.

Figure 1. Remote patient-centered studies revolve around the patient.

Remote Patient-Centered Trials: At a Glance

Open enrollment	Limited sites and centralized management	Data collection
• Patients are recruited and enrolled without regard to their proximity to a study site • Any patient with adequate access to the required technology (telephone, internet, smartphone, etc.) can participate	• Uses a limited number of sites (typically one per country) handled by a single "virtual" study coordinating center under the direction of the PI(s) • The study coordinating center facilitates all research activities, including recruitment, screening, informed consent, enrollment and data collection • PI reviews data as it is collected, monitoring the health and safety of study participants	• Data collection is facilitated by the study coordination center • Can include many types of data, both qualitative and quantitative • Can collect primary data from a wide variety of sources, including: ➢ Patients or caregivers ➢ Health care providers ➢ EHR, other databases ➢ Laboratories ➢ Home health agencies

Source: Covington et al.

Table 1. The design and operational elements of remote patient-centered research.

a limited number of study sites coordinated by a single-study coordination center; and data collection from multiple reporters and sources (see Table 1).

Patient engagement

In remote patient-centered studies, awareness and recruitment activities are targeted directly to patients to engage them in the research process. Interested patients typically contact the study via a study website or contact center where they learn more about the study and how they can contribute and participate, if eligible. Eligible patients then self-enroll directly in the study without visiting a traditional study site. Once enrolled, patients provide study data and/or grant permission for their treating healthcare professionals (HCPs) to provide study data. Patients need not be treated at a particular study site by the trial's principal investigator (PI) to enroll. Any eligible patient who is interested in participating and who has access to the required technology (telephone, Internet, smartphone, etc.) can participate in a remote patient-centered study, even those who live in rural areas or who are unable to travel (e.g., elderly, disabled, infants). This approach has potential to maximize engagement and enrollment of all eligible patients. For example, one study found that 69% of subjects who had participated in a remote Internet-based clinical trial reported that they would prefer to participate in this type of trial again rather than to participate in research that used other modes of data collection.[8]

Limited number of sites facilitated by a central study coordination center

Because patients are not required to visit a particular site, there is often only a single site or, for global studies, a single site in each participating country, to manage regulatory submissions. Studies are managed centrally by a remote study coordination center that facilitates all research activities, including recruitment, screening, informed consent, enrollment, and data collection. A medical team, led by the PI, monitors the health and safety of study participants by reviewing all data as they are reported in real time. By relying on a single site or a limited number of sites, the remote patient-centered approach is highly cost-effective, given that cost estimates for management of an active site range from $1,500 to $2,500 per month.[9]

Data collection

In remote patient-centered studies, it is possible to collect many types of data, both quantitative and qualitative, from a wide variety of primary sources. Unlike site-based studies, data are not collected by investigators during site visits, but rather through the central study coordination center. Remote patient-centered studies support data collection directly from multiple sources, including patients themselves, caregivers, HCPs, electronic health records (EHR), existing registries, databases, laboratories, and biospecimen repositories. Depending on the design of a study, collected data can include basic demographic information; anthropometric, biological, and laboratory measurements; medical, family, occupational, and behavioral histories; disease status and natural history; drug treatment information; quality-of-life, disease-related disability; and treatment satisfaction information.

Stakeholder engagement

Remote patient-centered studies facilitate the engagement of stakeholders throughout study design, recruitment, and operation. Key stakeholders include patients themselves, caregivers, doctors, researchers, advocacy/support groups, foundations, research consortia, government organizations, and representatives from biopharmaceutical companies with

Case Study: Pfizer's REMOTE

Pfizer conducted REMOTE (Research on Electronic Monitoring of OAB Treatment Experience), the first "virtual" randomized clinical trial, in 2011. This pilot project, conducted under an approved IND following review by FDA, used mobile phone and Web-based technology to recruit and enroll subjects and collect study data without visits to clinical sites. The trial was designed to evaluate safety and efficacy of a treatment for overactive bladder. By comparing REMOTE results to a previously completed Phase IV study, the sponsors hoped to determine whether Internet-conducted research could replicate results of a traditional trial. The goal was to validate Internet-based approaches with potential for "putting research within reach of more diverse populations ... to advance medical progress and lead to better outcomes for more patients."[4] Although the pilot inspired great interest, REMOTE failed largely due to lack of recruitment. Reported problems included patient concerns about putting large amounts of health information online, burdensome online research processes, and lack of "human" support through a study contact center. The study was revamped, based on patient feedback, to include call center guidance to support subjects during initial enrollment steps. Recruitment increased, but the study was discontinued due to the early delays. Sponsors announced plans to re-launch REMOTE in Europe at a future date.[13]

Pfizer's REMOTE study demonstrates that:

- It is possible to design remote patient-centered, randomized clinical trials that are acceptable to regulatory agencies, IRBs, and ECs.[14]
- Relying solely on technology, without human-to-human interaction, can negatively impact participation.[13]

potential therapies in their pipelines. Empowering stakeholders to play an active role in the study, including participation in advisory committees and protocol development, can greatly improve overall success.

The direct-to-participant approach of remote patient-centered studies and the ability of the remote study coordination center to facilitate global communication make these studies ideal for engaging stakeholders. Study coordinators provide ongoing around-the-clock support via email and telephone to data providers. An investigator-led medical team reviews data in real time to monitor patient safety and data quality. Sophisticated information technology platforms can be used to support these functions while integrating multiple data streams and accommodating the participation of multiple stakeholders.

Addressing research challenges using the remote patient-centered approach

Recruitment

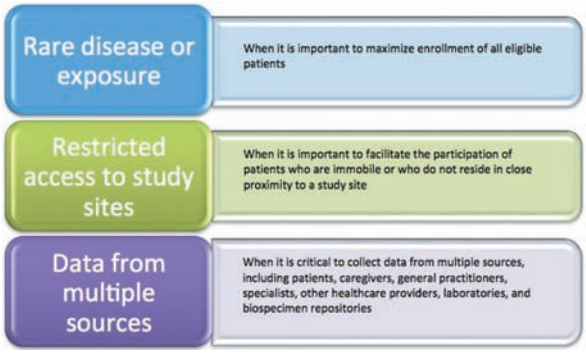
Recruitment is one of the greatest challenges faced in clinical research. A recent study found that 37% of sites under-enroll, and 11% fail to enroll a single patient.[10] Unlike site-based studies that recruit only patients treated at particular preselected sites, remote patient-centered studies can include patients without regard to proximity to a site. Thus, recruitment activities must be targeted directly to patients in addition to other stakeholders and data reporters, such as HCPs and pharmacies. This multi-pronged recruitment approach can be complex and requires expertise to design and implement recruitment strategies. Recruitment efforts should be customized to the population of interest. For example, Internet and social media can be used to reach younger patients, whereas television, radio, and print media can be used to reach older patients. To identify and contact potential subjects, researchers also can leverage disease-specific entities, including registries, research consortia, foundations, advocacy and support groups, and patient communities. Recruitment efforts to reach healthcare providers may include medical and scientific journal advertisements and articles, medical and scientific conferences, and medical websites.

Retention

Along with recruitment, the retention of patients in clinical research studies is an enormous challenge.[10] Key obstacles to retention include reporter burden, participant privacy concerns, and lack of incentive. Remote patient-centered studies can be designed to maximize retention by engaging patients and other data reporters throughout the study, streamlining processes, minimizing reporter burden, providing ongoing support, and sharing data among stakeholders. Human data sources, whether patients, HCPs, or caregivers, are vulnerable to survey fatigue. Cumbersome questionnaires and case report forms can dampen participant enthusiasm and provoke study dropout. When designing a trial, the primary and secondary endpoints of interest should be selected carefully and the data collected should be limited to only the information necessary for analysis of these endpoints. Data collection processes can be tailored to study-specific needs and made simple and succinct. Alternative data sources such as EHRs should be considered whenever possible to minimize the burden on those reporting data. For example, electronic data capture (EDC) methods can be used to streamline the collection of data from medical records, laboratory data, and biological samples, while electronic patient-reported outcomes (ePRO) systems can streamline the collection of data directly from patients.[11]

Patients and HCPs are concerned with maintaining the privacy of their information. Some are wary to share online

Scenarios Best Suited



Source: Covington et al.

Figure 2. Situations ideally suited for a remote patient-centered study.

and are more comfortable providing the information over the phone. Just as in site-based studies, appropriate safeguards should be put in place to ensure that data are protected. Thoughtful pairing of technology with live contact center personnel is often required to obtain an effective balance between efficiency and patient security.

Patient attrition also can be lessened through incentives. Where allowed, monetary incentives can facilitate retention. Remote patient-centered studies that do not require the patients to travel to a site often are less burdensome and could potentially require less incentive for participation (i.e., payment for travel to the site). Additionally, remote patient-centered studies are well suited to provide non-monetary incentives through data sharing. The direct-to-participant nature of remote patient-centered studies allows for dissemination of disease-specific communications, such as periodic newsletters and study results. These can be effective methods to improve retention of patients, who are especially motivated by information pertaining to their diseases.

The remote patient-centered model is ideal for streamlining processes and maximizing the participation of patients identified through direct-to-patient recruitment. Centralized operation via a remote study coordination center allows the processes of screening, informed consent, and medical record release to be performed remotely. All patient interactions are done by the same team at the coordinating center at the patient's convenience and, ideally, use the patient's preferred method of communication (e.g., telephone, Internet, smartphone, etc.).

Analytical issues

From an analytical perspective, the self-selection of participants in remote patient-centered studies can threaten the external validity of study results, as several researchers have noted and discussed.[12] Essentially, patients who voluntarily self-enroll represent a "convenience" sample of the population and may be different from the general population in terms of certain demographic or disease-related characteristics. For example, in a remote patient-centered study recruiting patients only from an online patient community (e.g., PatientsLikeMe, MediGuard.org, Inspire), it is possible that patients who enroll are more Internet savvy and interested in health information than the general population. Hence, results may be less generalizable than those of studies with a random selection of participants. Combining different methods of recruitment and offering more than one mode of participation and data collection improves the generalizability of results. As Internet recruitment technology and strategies continue to evolve and the population with the facility to use this technology broadens, concerns about the generalizability of results from this type of study should subside.

Technology issues

Success of the remote patient-centered approach is dependent upon a thoughtful blend of technology and human experience. Remote study coordination centers may require sophisticated information technology platforms for implementation and operational efficiency. The contact support staff tasked with managing the study must be experienced with the platform and able to guide participants through all processes of the study. Remote clinical trial designs are in their infancy, and few pharmaceutical companies and contract research organizations (CROs) currently possess the technology and experience needed to effectively manage these studies and serve as a study-coordinating center. Technology platforms that offer patient recruitment, screening, consenting, and data management functions within one efficient package are ideal for remote patient-centered studies, particularly if they include mobile device capabilities (e.g., enrollment via smartphone) and automated data management features (e.g., email reminders). Experience with these platforms and the ability to tailor them to fit study-specific needs undoubtedly will improve operational efficiencies.

Regulatory issues

There is little official regulatory guidance on designing and conducting remote patient-centered studies. As would be expected, remote patient-centered studies that are observational or that include non-product interventions face fewer regulatory and ethical hurdles than studies that include product interventions. Policies and processes vary by country and region, so remote patient-centered studies require consultation with the appropriate regulatory bodies as early in the research process as possible. In a global study, it may

be worthwhile to name a PI for each country or region included to facilitate the submission and review of regulatory and institutional review board (IRB)/ethics committee (EC) documents.

Remote patient-centered studies that can address the intricacies involved in conducting global studies offer great advantages in accessing patients and harnessing global resources. Study coordination centers must be prepared to support participants from around the world by accommodating cultural and language differences. The positive effects of tailoring communications to the personal preferences of the participants and providing prompt, courteous, and accurate support cannot be underestimated.

Situations ideally suited to the remote patient-centered study approach

Situations ideally suited to the remote patient-centered study approach involve patient populations that are difficult to reach using traditional site-based studies and/or that require data from multiple sources (see Figure 2 on page 33). The remote patient-centered approach is particularly valuable when studying rare diseases or rare exposures, where it is critical to maximize enrollment of all eligible patients. This approach is also useful when it is important to facilitate participation of patients who may have difficulty traveling to a study site or who do not reside in close proximity to a site.

The remote patient-centered approach is also useful when it is critical to collect data from multiple sources, including treating HCPs, specialists, patients, and caregivers. The study coordination center can facilitate the collection of data directly from the patient and his/her primary healthcare provider, specialists, and caregivers to allow the collection of data from the most applicable source of that particular data. For example, in a pregnancy registry, prenatal data can be collected from the pregnant woman's obstetric healthcare provider and the neonatal data can be collected from the infant's pediatrician.

Conclusion

With the industry's ongoing emphasis on efficiency, effectiveness, and timeliness, remote patient-centered studies are gaining more prominence and appear to be on the path to becoming an important part of clinical research going forward. Although they offer such advantages as maximizing enrollment and reducing study timelines and costs, those benefits are countered by potential regulatory, operational, and analytical challenges.

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Transforming Clinical Operations with a Fully Integrated eTMF Operating Model

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EVENT OVERVIEW:

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Bryan Ennis
Director
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Key Learning Objectives:

- Explain the importance of introducing eTMF technology early in the development cycle
- Describe the importance of a true multitenant eTMF application for ubiquitous access
- Understand why a robust and fully defined eTMF process can better help manage risk with fewer resources

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Risking it All? Going All in on RBM Adoption

Sherraine Hurd, Stephen Nabarro

Cancer Research UK applies risk-based monitoring across its entire trial portfolio. What were the results?

"Only those who risk going too far can possibly find out how far they can go." – T.S. Elliot

Cancer Research UK (CRUK) followed such advice when it decided to have its Center for Drug Development (CDD) adopt a risk-based monitoring (RBM) approach across its entire portfolio of clinical trials. This decision has revealed how risk-adjusted approaches can bring greater than 20% efficiency savings in the monitoring of early phase oncology trials, which were previously believed to be unsuitable for RBM.

CRUK funds half of all cancer research within the UK and provides research into 200 types of cancer across all age groups.[1] Within CRUK, the CDD features a Phase I portfolio and has completed more than 140 clinical trials, leading to five new medicines on the market.[2] The new CRUK research strategy is to accelerate progress and see three-quarters of cancer patients surviving the disease within the next 20 years.[3] It's, therefore, vital that the CDD remains innovative, pioneering new treatments to beat cancer sooner.

Embracing RBM

Though the U.S. Food and Drug Administration (FDA) released guidance on the expanded use of RBM in 2011,[4] there was still reluctance on the part of sponsors to take on a full-scale risk-based approach. Many were concerned that failing to conduct 100% source data verification (SDV) could lead to something being missed and the validity of trial data being compromised. In general, sponsors had misconceptions about the potential benefits of identifying, targeting and reducing risk.

This attitude, however, is starting to subside and more sponsors are beginning to explore and adopt different methods of RBM, including the CDD at CRUK. All of the trials CDD conducts are early phase oncology, which are inherently high risk; but the decision was made to embrace RBM to gain real benefit from the process. On-site monitoring can typically account for 25% to 30% of the overall cost of a clinical trial, so by setting an aim of reducing the frequency of our monitoring visits by 20%, we calculated a 6% savings on the cost of running a trial. From a business perspective, we calculated we could potentially open up another six to 10 sites, which would optimize our recruitment strategy. In reality, those sites that were classed as high risk would continue to have a high monitoring visit frequency, for example, every four to six weeks; however, those that were classed as low risk would be able to have a significant reduction in the monitoring visit frequency. By adopting RBM, we felt it would be a more efficient use of resources by allocating them to where they are needed most.

Moving to RBM

For many years, like most in the industry, CRUK adopted the same approach to monitoring; a one-size-fits-all approach driven by standard operating procedures (SOPs) with 100% SDV and conducting monitoring visits every four to six weeks. This meant a huge burden for the clinical research associate (CRA) to verify all source data against the

CRF, as well as attending regular monitoring visits to those sites with very little or no activity.

However, based on the guidance provided by FDA, the Medicines and Healthcare Products Regulatory Agency (MHRA)[5], the European Medicines Agency (EMA)[6] and Trans-Celerate BioPharma[7], we came up with our own approach to RBM that was piloted and successfully rolled out across the CDD in January 2014. The main aim was to reduce the number of monitoring visits by 20% across the portfolio as a whole, which was successfully achieved. This article discusses the steps put in place to make RBM "business as usual" within the CDD.

Our RBM process (Figure 1) is separated into three key themes—risk assessment, data surveillance, and dynamic monitoring.

Three-Pronged Process

Source: Hurd et al.

Figure 1. The three areas that make up Cancer Research UK's Center for Drug Development's risk-based monitoring approach.

Risk assessment

All projects and sites are now assessed for their specific requirements (for example, the visit schedule for patients during the study) and individual level of risk. The monitoring visit frequency and targeted SDV (tSDV) plan is then set based on the risk level identified within the study-specific monitoring guidelines. We no longer consider it appropriate to apply the same frequency of monitoring visits for each study.

> **All of the trials CDD conducts are early phase oncology, which are inherently high risk; but the decision was made to embrace RBM to gain real benefit from the process.**

A risk assessment (and corresponding score) is performed at both the project level and at each individual site level prior to the initiation of a study, and is then reviewed and updated on an ongoing basis (at least every six months) throughout the lifecycle of the study. We created a risk assessment tool within Microsoft Excel that is able to capture various risk criteria such as protocol deviations, data quality, AE/SAE reporting, etc. that are defined as objectively as possible. A score of 1 (low risk), 2 (medium risk), or 4 (high risk) is assigned for each criterion and a total score is established. Table 1 (see page 38) shows the criteria for two examples; data entry/query resolution and protocol deviations:

The inflated score of 4 for high-risk criteria is something we amended after the pilot to make sure that if a criterion was high risk, it significantly influenced the overall risk score and level assigned to the site. Each site may be viewed as low, medium, or high risk depending on the overall score received (a total of ≤ 23 is a low risk site; a total of 24-30 is a medium risk site; a total of ≥ 31 is a high risk site). If any one criterion is assessed as being high risk, then the overall risk cannot be low. It is important that the clinical study team revisit the risk assessment on a regular basis throughout the trial to ensure that the risk score and resulting monitoring approach is adapted to the changing quality of site performance.

All decisions, justifications, and mitigation steps surrounding the score are documented on a risk timeline. We take the stance that sponsors should consider the regulatory authorities as the "client" of their RBM approach, and, therefore, the risk timeline document is vital as it acts as the audit trail and allows inspectors to look back at any historical scores, and piece together the decisions taken and justification provided by the clinical study teams throughout the trial. The risk timeline document has been completed for a number of studies where the scores have been adjusted (or not) based on various criteria and study-specific justifications. Table 2 demonstrates the risk score for a particular study (single center) assessed in July 2013, January 2014, July 2014, and September 2014.

From the example provided in Table 2 (see page 40), it can be seen that the score has been assessed at six-month intervals and then more frequently due to new information which triggered another risk assessment in September. The study team documented its concerns, justifications, and mitigation plans in order to support the score assigned, resulting in it becoming a high risk. This is a good example of allowing an auditor to see the logical steps and decisions made at each assessment. We want to avoid being "ruled" by the metrics, so the risk score is only used as a guide and ultimately it is at the discretion of the study team as to what risk is associated with a study or site (as per the July 2014 entry in Table 2).

The risk score is also reviewed by quality assurance (QA) to determine the audit program for the year ahead. One

Risk Criteria Comparison		
	DATA MANAGEMENT QUERIES/ SUBJECT	**PROTOCOL DEVIATIONS**
Low (1)	On average, data entry within double the time period specified in trust agreement (i.e., if five days for completing data, entered within 10 days) AND average query days open to first answered is <10 days	Non-compliances only since penultimate review
Medium (2)	Poor quality data, or either a) average data entry not within double the time period specified in trust agreement, or b) average query days open to first answered is >20 days	High frequency of non-compliances or deviations not considered reportable in the CSR since penultimate review
High (4)	Poor quality data AND either a) late data average data entry not within double the time period specified in trust agreement, or b) average query days open to first answered is >20 days	Deviations considered reportable in the CSR; or serious breach seen since penultimate review; or start of study if less than two reviews performed

Source: Hurd et al.

Table 1. The risk criteria breakdown for two specific examples.

uexpected benefit of implementing RBM at CRUK is greater collaboration between our clinical operations and QA teams.

Data surveillance

Ultimately, we have increased the interaction between our clinical data managers (CDM) and site staff, as we found that the CDMs were an underutilized resource when it came to RBM and that their skill sets are perfect for the central monitoring role required. The CDMs contact sites on a regular basis (and vice versa), whether it is to notify them of outstanding data and queries, or whether sites need help with entering data in study-specific forms or need technical advice.

Delayed data entry is also something many experience in the industry. Despite having electronic data capture (EDC) and the ability to access data in real time, this is rarely the case and can lead to a data entry backlog. CRAs are then unable to make the best use of their time at the site if data has not been entered when they attend a monitoring visit. We, therefore, came up with a tool to help reduce this additional burden to the CRA: the data entry schedule (DES). This helps facilitate prompt data entry of key study data to allow the CDM to review and clean the data in a timely manner. The DES does not supersede any contractual obligation for data entry, instead it complements it. The tool is created and overseen by the CDM, with input from the study team to agree on suitable and realistic timeframes for data entry. It is then agreed with the site, ideally at the site initiation visit (SIV), so they are aware of the data entry expectations and have an opportunity to discuss any concerns. The CDM monitors this throughout the study and contacts the site when the timelines have been missed.

Since introducing the data surveillance procedures, CRUK has received some positive feedback from site staff via a survey (e.g., 75% of site staff responded that they found the DES useful). Many of them now contact the CDM directly when having issues with data entry or query resolution; some inform the CDM when they are going to be out of the office, thus impacting the DES; some even request calendar invites to be sent so they act as reminders for data entry based on the DES. This is all very encouraging and reiterates the fact that the CDM can play a more central role in the RBM process.

We now put greater emphasis on CRAs remotely monitoring trial data, taking advantage of the fact that there is EDC and data readily available. CRAs perform remote monitoring in line with the study-specific monitoring guidelines and may raise queries or contact site staff regarding any issues. This allows the CRA and site staff to focus their time on other activities and plan future goals.

Dynamic monitoring

The frequency of monitoring visits and level of tSDV are determined for an individual site based on the associated risk score and category (low, medium, and high) assigned using our risk assessment tool. This is documented in the study monitoring guidelines, which also defines critical and non-critical data. The level of SDV performed on critical data is 100% for all patients, whereas the level of SDV performed on non-critical data is variable depending on the risk score assigned. The CRAs also utilize the freeze function on the EDC database as a means of tracking the status of SDV, which has been found to be very useful.

During the pilot phase, we sought input and feedback on our processes and tools from the MHRA and EMA regulatory agencies. Both provided valuable feedback in order for us to make any adjustments to the existing process. A common discussion among delegates at RBM conferences is how little guidance and support the regulatory agencies provide on this evolving field. This is not something that we found, and we were surprised when the EMA told us we were the first sponsor that had sent them a RBM methodology to review.

To support the use of RBM, we also had a number of study and system audits conducted on trials where RBM was piloted. There were no critical or major findings that implied a reduction in data quality, patient safety, or trial integrity, which provided evidence that we had implemented the RBM process correctly. As our first attempt into RBM, we acknowledge it is a modest step. In due course, a larger leap, such as reduced SDV of critical data as well as non-critical data, could be taken. We decided against taking too big of an initial jump because of the risk of impacting patient safety, for

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Risk Assessment Scorecard

DATE	SITE-SPECIFIC	RISK SCORE & RISK LEVEL AS PER RISK ASSESSMENT TOOL	FINAL RISK LEVEL DETERMINED BY PROJECT TEAM	CONSIDERATIONS/ CONCERNS IDENTIFIED:	JUSTIFICATION FOR RISK LEVEL & ANY MITIGATION STEPS OR MANAGEMENT STRATEGIES REQUIRED/ ALREADY IMPLEMENTED (INCLUDING ANY ADAPTATIONS FROM TRADITIONAL GCP REQUIRED)
July 2013	Site X	25 (Medium)	Medium	NA	Project risk is high mostly due to novelty and known safety risks of the compound as well as being an FIM study. Site assessed as low risk initially, as site is well known to be a good site as the CDD works with the site relatively often. Pharmacy was assessed as low risk.
Jan 2014	Site X	30 (Medium)	Medium	After discussion within the study team meeting, the biggest concern is the clinical data. AEs were not entered into the CRF prior to a dose-review meeting, and AE query resolution where medical input at site is required is problematic causing delays.	Risk score has gone up from 25 to 30. Data quality is high. The risk score has also increased due to the recruitment rate being as expected, new site staff, and the occurrence of protocol deviations. The result of the risk assessment has been communicated to the CI, and ways of improving medical query resolution and data entry were discussed. The monitoring guidelines have been updated. No major change except to reduce the requirement of 100 % SDV from 1/3 patients to one per cohort from Cohort 4 onwards in stage 1, and 1/6 in stage 2 as transcription accuracy is high.
July 2014	Site X	33 (High)	Medium	A continuing concern was identified of the site data manager missing the transcription of a large proportion of AEs into the CRF. When on site, the CRA spends a lot of time going through the source notes to pick up these unreported AEs.	After reviewing all the data, the study team members decided the site should remain as medium risk. There are no issues with data transcription and there would be no perceived benefit in increasing the amount of non-critical SDV. As highlighted, there are issues with AE identification and a risk mitigation plan has been agreed, for the CRA to discuss this with the site data manager at the next visit. If no improvement is seen at the next MV, the CSM will escalate this issue to the PI for resolution, where improvement will be expected to be seen within two months. In the meantime, the CRA needs to review all patient source notes prior to dose escalation meetings.
Sept 2014	Site X	35 (High)	High	The previously identified concern of the site data manager missing the transcription of a large proportion of AEs into the CRF persists, and recently this has had an implication on the study timelines. An unreported AE meant that deemed a patient unevaluable for the dose escalation was not reported at the time and only identified the week prior to the planned dose escalation, during a monitoring visit.	Due to the issue of unreported AEs, this site has been classified as high-risk. The previously documented risk mitigation plan was followed by the team, and after the discussion between the CRA and the site data manager, the proportion of reported AEs has reduced, but remains at around 20%. The CSM will escalate this to the CI shortly to discuss what process improvements need to be made at the site. As the site now falls into the high risk category, % of non-critical SDV performed should be increased, however, after a discussion between the CSM and CRAs as transcription accuracy is high, this was thought to add non-benefit, and take time away for the CRAs focusing on reviewing the source notes for unreported AEs. SDV frequency will, therefore, remain at the medium-risk frequency. It was agreed that monitoring-visit frequency should increase to once every three weeks whilst patients are within the DLT assessment period, to ensure that unreported AEs are detected sooner by the sponsor. It was also agreed to allow a minimum of three days between a monitoring visit, where dose escalation data is monitored and when the data listings are run. This allows time for unreported AEs to be entered into the CRF after a monitoring visit.

Source: Hurd et al.

Table 2. The risk score for a specific single-center study assessed at four six-month intervals.

example, only detecting an ineligible patient via SDV after they have completed their treatment and their data has incorrectly been used as evidence for dose escalation. We have also provided clear communication pathways with sites to reiterate their key roles and responsibilities remain as per International Conference on Harmonization (ICH) good clinical practice (GCP); site staff are accountable for the accuracy and completeness of the data entered into the eCRF. This is especially important in relation to targeted SDV, as the CRA will not necessarily double check that all data has been entered correctly. We have emphasized the importance of prompt data entry to allow our medical advisors and pharmacovigilance department to review "live data" in the eCRF throughout the study, as well as reinforcing the fact that clear communication is needed for any potential issues that may arise between monitoring visits.

How the RBM process is working?

We have identified several performance-related measures of success in order to help establish whether our RBM approach is working. Some of these are obtained from our EDC database, others are feedback in the form of questionnaires and general adoption of the process. At the beginning of the pilot, we established some baseline measurements and were then able to re-measure them post-pilot. Overall, we found:

- The average time taken for sites to resolve data queries (based on eight studies) prior to the pilot was nine days. However, post-pilot, this reduced to seven days. This reduction supports the fact that using the CDMs to contact the site directly regarding the queries helps reduce response time.
- A significant increase in the number of occurrences where site staff contacted CDMs directly in relation to queries, data entry, and general database issues post-pilot, with a baseline measurement of zero prior to the pilot.
- CRA productivity during monitoring visits increased by 55%. Prior to the pilot (100% SDV and monitoring frequency of every four to six weeks), the average number of eforms SDV'd were 61 per day. However, post-pilot (tSDV and adapted monitoring frequency dependent on risk score), the average number was 94 eforms per day.
- From questionnaire feedback, 75% of site staff found the data entry schedule useful, 80% found the direct contact with data management beneficial and experienced site staff noticed that CRAs had more time at site to support them with other tasks.

The measures of success will still be monitored and re-assessed in the months ahead to continually evaluate the benefits of RBM. RBM takes a large proportion of people out of their comfort zone, as it is different from what we were accustomed to historically. Therefore, in order to promote the work and benefits of using RBM, our pilot, processes, and results were continuously presented to the rest of CDD. Naturally, there were late adopters within study teams who were skeptical of using risk to determine monitoring visit frequency as well as conducting tSDV, and so this was a challenge in itself. We decided to pilot RBM on studies where a CSM was involved in the RBM working group to demonstrate how to conduct the risk assessment, tSDV, the use of the DES, etc. We also included CRAs that embraced change, which helped to provide confidence in the new process. During the pilot and afterward, a clear communication path was maintained with everyone in CDD, which helped with any disruption to normal practices. However, as RBM is now business as usual, an associated policy document has been created as well as a corresponding guidance document. The policy helps cement RBM working practices at the CDD.

We have also conducted a number of external presentations and case studies to various organizations highlighting the fact that RBM can be applied to early phase studies and that expensive software is not a prerequisite in order to conduct RBM. So far we have received positive feedback on the work we have carried out and are happy to continue to share our processes and outcomes.

To those that have not considered adopting RBM or are still uncertain, give it a try. After all, "Only those who risk going too far can possibly find out how far they can go."

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Exposing Patients to the Bigger Mobile and Digital Health Picture

Could there be a greater commitment to engage people about clinical research—prior to any medical need arising?

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The World Health Report 2013 argues that universal health coverage cannot be achieved without the evidence from scientific research, and in order to better manage healthcare, clinical research needs to keep up-to-date and advance in line with society in general. Without clinical research, global health would falter and decline, but perhaps the importance of this relationship is not well recognized.

Two-way movement of information is critical and underpins both clinical research and healthcare. Better engagement leads to more informed and empowered patients, and ultimately improves patient outcomes. An opportunity, therefore, exists to truly embrace the mobile and digital revolution, and utilize its full potential in 21st century clinical trials.

As insufficient people are aware of clinical trials, could there be a greater commitment to engage people about clinical research—prior to any medical need arising? The science curriculums in our basic education systems don't adequately introduce this critical topic. Hence, we're missing out on the starting point in the healthcare communications chain—an opportunity to influence new ways of thinking, and establish a new generation of trial participants and future influencers.

Complicated medical language has long prevented easy access to healthcare, engendering an aura of "respect" and "reverence" to physicians. However, patients are becoming increasingly confident in searching online and asking questions—mobile and digital technology is enabling more digestible content (making medicine less exclusive, and healthcare more accessible for the masses).

The medical community is still learning to routinely embrace mobile and digital technology, although healthcare professionals (HCPs) are increasingly accessible through online "virtual" consulting. This may create new opportunities for clinical research awareness.

Today's youth has grown up in an information-loaded, technology-rich world, with data instantaneously accessible through the portable medium of their (smart) mobile phone. But what do patients really understand about mobile and digital capabilities in healthcare? Does the average person know that scale data can be collected via mobile, and the results viewed in real time by the HCP? Or that asthma sufferers can blow into a Bluetooth (to mobile) paired spirometry device, to help track their condition? I suspect that the public are largely unaware of how, where, and why mobile and digital technology is being used in clinical research and healthcare management, and what options are available already.

If popularized sufficiently through technology, could we anticipate greater understanding of clinical research, and generally improved healthcare management? With decreasing numbers of medically trained doctors, and a seemingly crisis-level escalation in some countries of chronic diseases, when it comes to health management, we need to embed a greater sense of ownership in everyone. We need to help ourselves, and that's where "mHealth" can put control into the patient's hands (e.g., digital access to public health campaigns, online interactive support programs, or mobile data collection for trials).

Just how far the mobile and digital health revolution can take us is unclear. It could reveal previously unknown facts through sheer data volume, or we may find that clinical research is changed through greater honesty, convenience, or control between HCPs and patients. Endless possibilities emerge. Imagine if all chronic sufferers were to give a health status on a given "World Mobile Health Day"; how powerful that "snapshot" would be.

Clinical research is just a building block in health management. But if we could "mobilize," educate, and engage everyone, then the bigger picture would be clear. Let's tell the patients.

KEYNOTE SPEAKER

BESTSELLING AUTHOR

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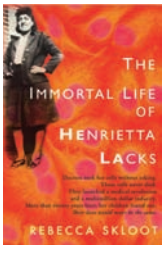

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