Study Start-Up

TRIAL DESIGN
STREAMLINE AND IMPROVE START-UP

INFORMATION TECHNOLOGY
ELECTRONIC DATA CAPTURE

SUBJECT RECRUITMENT
PHARMACISTS AND RECRUITMENT

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To begin developing an analytics approach to monitoring, a company must first investigate its data sources to identify risk identifiers, develop a risk algorithm around these risk identifiers and data flows that will feed into the algorithm, establish a governance structure, and identify pilots for the new operating model. As new trials begin, a company can gradually transition all of its therapeutic areas to risk-based monitoring. As the risk-based monitoring program develops, change management and communication will be essential to its success.

For the algorithm to work properly, the required data must flow into a centralized database. Companies pursuing an analytics approach to monitoring should evaluate current technologies in the clinical platform to identify gaps in the type of data they are collecting. Current technologies, vendor portals, and query tools will already be capturing some of the data points; however, other points will be missing, so technology will have to be adapted or developed to fill in the gaps.

Pharmaceutical companies and contract research organizations with broad risk profiles across their portfolios are expected to see the greatest cost savings in moving to a risk-based monitoring approach. Trials that typically yield the most significant savings are large Phase II or III development studies with drug safety profiles that are mild to moderate.

Robert Franco, Partner; Mark Hronec, Director; and Brian Slizgi, Senior Associate, all with PwC’s Pharmaceuticals and Life Sciences Industry Practice.
Some see a map of potential sites.

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EU Enlargement With Croatia Comes Under Scrutiny

European Union enlargement with Croatia—as well as the latest changes to clinical trial legislation, innovation (products in the pipeline), transparency, and implementation of the pharmacovigilance legislation—will be discussed in-depth during a regulatory town hall meeting at the Drug Information Association’s 26th Annual EuroMeeting.

As an indication of the importance being attached to the special session, Guido Rasi, Executive Director of the European Medicines Agency (EMA), will chair the event, along with Christa Wirthumer-Hoche, Deputy Head of the Austrian Medicines and Medical Devices Agency. Attendees can put burning questions to the panel of expert regulators, including Viola Macolic Sarinic, Head of the Agency for Medicinal Products and Medical Device in Croatia, which joined the European Union as its 28th member state on July 1, 2013.

According to an EMA statement issued in July, “Croatia is now part of the European medicines network and its representatives are fully involved in the activities of the seven scientific committees of the EMA as well as the agency’s other activities. In January 2011, the EMA, together with the Croatian national competent authorities, started a pre-accession linguistic review of product information for centrally authorized medicines in the Croatian language.”

The plan is to phase in European Commission (EC) decisions on centrally authorized medicines, thereby avoiding delays in the supply of medicines in Croatia. Also, the aim is to avoid peaks of activity for regulators and industry around the time of accession. Delegates at the EuroMeeting, to be held in Vienna March 25-27, 2014, will find out whether this strategy has worked.

Over 3,000 professionals from industry, government, and academia, plus students and representatives of patient groups, are expected at the congress. There will be more than 100 sessions in 17 parallel themes, and 350-plus expert speakers, including representatives from the EMA, EC, FDA, and European national regulatory agencies. In addition, there will be 14 pre-conference tutorials and over 170 exhibiting companies, the organizers noted.

A satellite meeting will take place about how to make Austria a more attractive research and industrial pharmaceutical location. Also, the clinical research track will focus on draft risk-based monitoring regulations, new technologies organizing aggregated sources of digital data, and how advances in behavioral sciences provide new responses to industry’s search for optimized clinical research paradigms.

“What are the lessons learned and benchmarks to date in this new era of clinical research?” noted joint organizers Clara Heering, Senior Director Project Coordination Center, Western Europe, Quintiles, Belgium and Carl Naraynassamy, Director of Explicator, UK in the DIA 2014 EuroMeeting preliminary program. “We need to ascertain that the paradigm shifts are founded on robust assessments of risk and evidence of qualitative and effective processes; verify that investigators, monitors, and project managers are empowered in their decision making; and satisfy ourselves that the greater reliance on digital data enhances patient safety and ethical conduct of clinical research.”

The e-clinical track will discuss how the past decade has increased the possibilities for speeding up, increasing quality, performing new types of studies and analyses, streamlining the data flow, and in general taking clinical development to the next level. The added value, implications and future perspectives of e-clinical will be presented in an understandable way to the various (non-technical) disciplines involved in pharmaceutical development, according to organizer Peter Stokman, Head Global Data Management & Standards Oss, Merck Sharpe and Dohme, Belgium.

Another session will look at how to involve and inform patients. It will give examples of what patients need to know about clinical trials, how to turn informed consent into an opportunity, best practice for patient advocates in clinical research today, how to effectively use social media and mobile devices to work with patients, and how to train patient advocates to be knowledgeable partners in clinical research.

“Well-informed patients and patient advocates have a key role to play in the implementation of patient-centered clinical research strategies and approval processes, access to treatments and treatment optimization approaches,” stated Jan Geissler, Project Director of European Patients’ Academy on Therapeutic Innovation. “In an era of growing demand and emphasis on both quality and sustainability of healthcare, it is critical to involve patients in the R&D process. In many disease areas, patients are already actively engaging in the many processes involved in the development of new treatments today, from contributing to protocol design, informed consent, and ethical review to the overall medicines development process, marketing authorization, and healthcare policy. Involving patients can accelerate research and make it more effective.”

—Philip Ward
TRENDS IN
Central Labs & Biomarkers
Biomarkers are Used for Multiple Purposes

According to FDA Guidance, http://1.usa.gov/1aSnezx, biomarkers can be used for a wide range of purposes, including, but not limited to, the following examples:

- Patient/clinical trial subject selection
- Assessment of disease state and/or prognosis
- Assessment of mechanism of action
- Dose optimization
- Drug response monitoring
- Efficacy maximization
- Toxicity/adverse reactions minimization

These areas fall under what Phase I through Phase III clinical trials examine. But what about pre-clinical or Phase 0? It is true that while biomarkers are of increased importance in clinical trials, as is the basis of the above-referenced guidance titled “Biomarkers Related to Drug or Biotechnology Product Development,” the foundation of personalized medicine and translational medicine, depends solely on biomarkers.

As recently as May of this year, Janet Woodcock, Director of the FDA’s Center for Drug Evaluation and Research, noted that personalized medicine has achieved mainstream status, accounting for more new drug approvals and promising pipeline candidates. As noted in this news report in Applied Clinical Trials, http://bit.ly/19JQQUY, Woodcock observed that this is particularly visible in developing new treatments for cancer, genetic disorders, and infectious diseases, as new therapies emerge that are particularly effective for limited groups of patients. But, she emphasized, the need to study ever smaller subsets of individuals requires new clinical research approaches.

These approaches, specifically, require stakeholders to “turn the clinical trial paradigm on its head” and for research organizations or coalitions to set up ongoing, standing trials to examine patient responses to multiple issues raised by test therapies and biomarkers for certain diseases or conditions.

In a recent proprietary research report regarding changes in clinical trials and drug development efficiencies, one respondent reported the use of biomarkers as a measure of the indication, which gives an idea of whether the drug works, and another noted that biomarkers are playing a big part in efficiencies and identifications above.

In this insert, the authors examine both the role of biomarkers in pre-clinical to Phase III trials, as well as the need for improved testing, storing, and examination of the biomarkers acquired in trials via a central lab. In fact, one can’t have a biomarker without a lab and as noted in ISR Re-
ports’ “Central Lab Market Dynamics and Outsourcing Performance,” in late 2012, respondents indicated that central lab services were projected to see the most growth over the next three years based on biomarkers and genomics. Specifically, “biomarkers from Phase IIb through commercialization” is expected to experience the largest rate of growth.

Further, the report noted the attributes that sponsors use to select a central lab provider, respondents indicated that “quality” (34%) is the single, most important attribute. When respondents were asked to select their top five most important attributes for selection, “quality” (65%) was followed closely by “sample turnaround time” (56%).

The interplay of market forces for the past few years in the biomarker and central lab space are driven primarily by the oncology area, as noted in both of our articles. However, that said, other therapeutic areas are starting to heed the call of personalized medicine and biomarkers and targeted therapies are in development for immunology, neuroscience, metabolic, and inflammatory diseases. Combine these with the already established oncology drug pipeline, it is apparent that these market drivers will be in place in clinical trials for some time to come.

**Figure 1.** When selecting a central lab service provider, respondents indicated that “quality” is the single, most important attribute.
Transfer of knowledge between pre-clinical and clinical research is necessary to deliver effective medicines to patients.

Translational Medicine and Biomarkers

Holly Hilton, Rand Jenkins, and Steve Lobel

Translational medicine (TM) is the emerging discipline involving the translation of laboratory findings into the design and implementation of early-stage clinical trials. TM focuses on translating pre-clinical data from in vivo, in vitro, and in silico research into the clinic to help design trials, determine methods, and choose the biomarkers. In addition, TM uses the data from clinical studies to feed back into pre-clinical experiments to improve future drug discovery. Biomarkers are an essential piece of the translational effort and critical to understanding an individual patient’s disease and response to experimental treatments. TM uses a very patient-driven approach to drug development and is a result of the practical application of the improvements made in biomarker discovery in the era of personalized medicine (PM).

Many pharmaceutical companies are introducing TM departments charged with the task of facilitating the transition of basic research into practical treatments and clinical trials. These organizational changes are based on the need for an improved, dynamic exchange of information between late pre-clinical efforts and early stage clinical trials.

Traditionally, oncology has been at the forefront of the biomarker development and PM. However, as technologies advance, fields such as neuroscience and immunological, inflammatory, and metabolic diseases are expanding their use of biomarkers for PM. Personalized medicine seeks to identify individuals who will receive the most clinical benefit and least harm from a specific treatment by targeting genetic or other targets associated with their disease. Enabled by technological advances and expansion of the use of biomarkers, researchers can stratify patients into disease subtypes and evaluate targeted therapies aimed at treating them. With the cost of developing a successful drug typically exceeding $1 billion, the need has never been greater to effectively translate pre-clinical research into the clinic and learn from early stage clinical trials.

Phase 0

Over the past 10 years, advances in early phase studies have focused on collecting and applying more clinical pharmacology data sooner to inform dose determination, endpoint identification, and patient selection in Phase II trials. Phase 0 trials are emerging, particularly in oncology, to help translate pre-clinical research into humans before Phase I. Phase 0 evaluations leverage the incorporation of biomarkers to gain more information from first-in-human experience.

In Phase 0, microdoses of experimental drugs are administered to volunteers. The dose is expected to be well below toxicity and efficacy points, but can be used to make an initial assessment of pharmacokinetics (PK) and pharmacodynamics (PD) effects. Positron emission tomography (PET) and accelerated mass spectrometry (AMS) imaging are used to assess drug distribution and other clinical pharmacology measures. Phase 0 biomarker evaluations can
provide direction regarding drug targets, mode of action, and pharmacology to make data collection in Phase I more selective.

**Phase I**

Traditionally, Phase I studies assess the safety, tolerability, PK, and PD of an investigational drug to determine dose, dose schedule, and route of administration. Phase I investigations use biomarkers to identify and recruit targeted patient populations, as well as evaluate patients’ response to drug treatment. Phase I evaluations are designed to inform Phase II endpoint selection, streamline trials to demonstrate proof of concept, and facilitate more efficient approval pathways.

**Patient stratification biomarkers.** Biomarkers that can identify patients expected to respond to a targeted therapy will increase the chance for delivering the right medicine to the right patient. Current targets include BRAF gene mutations in metastatic melanoma, HER-2 mutations in breast cancer, and ALK gene translocation in non-small-cell lung cancer. If preclinical research has not delivered patient stratification biomarkers prior to entry into humans, Phase I and Phase II data may be useful to discern them after treatment. Correlations between patient response and biomarker measurements can be used to retrospectively discover patient stratification biomarkers that have the potential to be used in later trials. This retrospective analysis is facilitated by a translational medicine team dedicated to extracting information from biomarker measurements.

**Pharmacodynamic biomarkers.** Monitoring patient response to therapy in Phase I is critical to determining the correct dose for Phase II. Biomarkers for toxicity and target engagement can help researchers decide upper limits of dosing. In healthy volunteer studies, biomarkers can also help predict response in patients where none is expected in non-diseased individuals. In targeted drug development, Phase I is the starting point for tissue collection, genetic profiling, antibody testing, and tumor typing that support clinical research and patient selection.

**Phase II**

Phase II trials are deemed “proof-of-concept” trials as the goal is to determine if the drug has the hoped for biological effect. Phase II determines drug efficacy and evaluates Phase I safety assessments in the expanded number of subjects. Biomarkers continue to play a critical role in Phase II trials. Safety biomarkers remain standard practice for monitoring adverse events. Patient stratification and pharmacodynamic biomarkers also continue to be assessed. A large panel of exploratory biomarkers that is assessed in Phase I trials can be reduced in Phase II to those that showed the most promise. Biomarkers that have been previously correlated with long-term patient outcomes can be used as surrogate or secondary endpoints.

**Summary**

Critical to translational medicine is the conversion of insights from pre-clinical research into early clinical trials. In addition, TM fosters ongoing evaluation of clinical biomarker data to both inform the next stage of trials and to provide feedback into additional pre-clinical studies. Pre-clinical data is used to predict a mechanism of action for the drug and choose biomarkers appropriate for patient stratification and response to treatment. Because pre-clinical models are known to be imperfect at predicting human response, the translational medicine teams must use biomarkers to measure as much information as they can as early as possible in the clinic. Further pre-clinical research can explore hypotheses generated from the clinical biomarker data to predict more effective biomarkers for the next stage of clinical testing. This translation of knowledge between pre-clinical and clinical research is necessary to design and run effective clinical trials and ultimately deliver effective medicines to patients.

**Holly Hilton,** PhD, is Director, Biomarkers and Translational Sciences, **Rand Jenkins,** is Director, Laboratory Operations, and **Steve Lobel,** PhD, is Vice President, Global Laboratory Operations all at PPD, 929 North Front Street, Wilmington, NC.
Central labs promote scientifically objective results, through independence of action on a contractual basis with the sponsor.

The Shift to a Centralized Lab Approach

John A. Laczin, MD

Testing drives drug development. From laboratory tests on patients’ specimens comes almost all the clinical data needed for a new drug application. How and where those specimens are collected, transported, stored, and analyzed impacts the quality and usefulness of the data they produce. In the past, most tests were processed by local, academic, and specialized testing laboratories and coordinated by each investigator. However, centralized testing is becoming an accelerated trend—one that uses advanced technology and global operations to concentrate clinical trial tests in a single, central laboratory.

In the past, most tests were processed by local, academic, and specialized testing laboratories and coordinated by each investigator. However, centralized testing is becoming an accelerated trend—one that uses advanced technology and global operations to concentrate clinical trial tests in a single, central laboratory.

Combining for consistency

The central lab core value is consistency. When local laboratories perform testing, their results will be different. In fact, if they were not, it would be suspicious. Central laboratory testing, on the other hand, offers “combinable data,” generated from the same analytic method platform to correlate and standardize results. The end product is that a result from a central laboratory is similar regardless of the facility it came from. In contrast, local laboratories use many different analytic methods, often breaking down into “low, medium, and high” between local labs. Less variation in central lab results also makes it easier for trial sponsors to assemble meaningful statistics. In the end, results from the central laboratory are easier to defend to regulatory agencies.

Sample collection kits drive consistency

Sample collection kits embody the goal of central laboratory consistency. For instance, a given test may be done on serum or plasma—different specimens—and each type of specimen will yield an answer, but that answer will be different from one to the other. Local labs pick the type of specimen that works for their own analytic method. But in a global clinical trial, that local lab will still use their local analytic method—which may be an alternate specimen type with its own bias. The central lab standardized specimen collection kit avoids such bias. The kit also contains every useful article necessary to obtain specimens and ship...
them back to the central lab. Thus, the standardized kit removes many possible variables from the specimen collection environment. In each kit, the set of collection components are specific to a particular patient visit—from screening at the first visit, through all other visits for the remainder of the trial. Special kits apply for retests, end-of-trial activities, anatomic pathology specimens, PK, biomarkers, and genomics. This standardization promotes another basic—and productive—central laboratory solution to specimen collection: recognition of the expertise of the investigator and staff who do the actual collection of the specimens. Collection methods and instructions can be optimized, training investigator staff in efficient specimen handling so the trial can begin enrollment with minimum delay, reach budget milestones, and deliver required data by meeting the unique needs and timelines of each protocol.

Oncology data: shifting from local
In recent years, we see a shift from local laboratories to centralized analysis in the support of oncology studies. Three main forces determine the pace of further progress: international regulatory harmonization of drug development, growth of global trials, and progress of cancer research. Key trends include increased analysis of “biomarkers” and greater regulatory pressure for global data combinability. The pace of adoption of central laboratory services in oncology trials depends greatly on the direction cancer research takes in the next few years. For pathologists, tumor heterogeneity—variability of a malignancy within itself—is increasingly recognized, and promises to complicate oncology for years to come. Central laboratories assist or improve the clinical trial process for oncology studies in several ways:

- Globally uniform sample collection kits, customized to each trial and paired with logistics support services, to ensure irreplaceable tissue biopsies arrive at the laboratories in optimum time and condition.
- Specimen management services to allocate and track patient tissue block samples through each step, regardless of sectioning type or placement on slides or in tubes.
- “Target enrichment” of anatomical specimens, to yield concentrated tumor tissue for use in downstream genetic and molecular testing, allied with digital imaging and special processing techniques.

Trends favor central lab model
But industry resistance to the central model persists. One traditional argument for the use of local laboratories is patient safety and dosing—but the central lab’s means and speed of reporting results improves constantly, and this actually enhances patient safety, while keeping consistency in analysis around the world. It’s the best of both worlds.

Finally, use of central labs holds out to sponsors something no local lab can. Time and again newspaper headlines trumpet irregularities traceable to individual persons whose scientific detachment was lost, whether for economic, personal, or sinister reasons. Central labs promote scientifically objective results, through independence of action on a contractual basis with the sponsor, transparency via a durable audit trail, and by being responsible to governmental regulatory bodies through licensing and certification. These conditions work to remove bias due to local pressure, whether cultural, economic, medical, political, or scientific. Thus, scientific objectivity in clinical trials results carries its own value by active work to avoid the accusation of and exposure to improper influence. The importance of this is self-evident, because in this industry the ultimate beneficiary of scientific objectivity is us.

John A. Laczin, MD, FCAP, is a physician and pathologist, boarded in both Anatomic and Clinical Pathology and the Director, Medical Affairs in Central Laboratory Services at Covance Inc., 8211 SciCor Drive, Indianapolis, IN, e-mail: john.laczin@covance.com.

The central lab’s means and speed of reporting results improves constantly, and this actually enhances patient safety.
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*Ad page corresponds to the September 2013 issue of Applied Clinical Trials.*
Japan Relaxes Clinical Trial Regulations; China Still Strict

Parexel’s President & COO Mark Goldberg sat down with Applied Clinical Trials for a quick discussion on the trials market in Asia Pacific.

What is the current global hotspot?

When you look at trends for where the newest opportunities are for sponsors, our clients, to sell their drugs certainly Asia Pacific is the biggest growth area. There are other emerging regions, certainly, but if you had to pick one, Asia Pacific would be the one you would pick. Not as much India at the moment.

Within Asia Pacific where do you see the most growth opportunities?

Lots of growth in Japan at the moment, driven by the fact that the government is really trying to address their historical drug lag. Approvals are happening sooner and there is more flexibility about the inclusion of data from other Asian populations. Japan is a little more relaxed now in terms of trial participants, not to the point that they would be willing to look at Western data but certainly from different Asian countries.

The pharmaceutical market in China is certainly on the rise. Is there anything interesting going on there from the trial perspective?

In China you have a lot of demand for clinical trials. You have a reshuffling of the regulatory authority, which is creating some delays in getting trials started. Right now it is taking between 12 and 24 months to get new trials started in China. It depends to what degree the indication is viewed as a priority by the Chinese government for their population.

In the case of biologics, all phases of development, Phase I through Phase III, have to be done in China. This is relatively new requirement in the biologic space. For other indications that is not the case and you can include a sub-population in China within a larger global study. You have to agree with the Chinese authorities about how many patients from China would be required to meet their needs for local registration.

Another aspect that makes conducting trials in China a little more difficult is the fact that to be an investigator you have to be certified by the government. There are still a relatively limited number of certified investigators. I think China is picking and choosing a little bit on what their priorities are.

—Timothy Denman

DATA ANALYSIS

Investigator Non-Compliance and Fraud

The number of complaints filed with the FDA for investigator non-compliance and fraud rose rapidly in the late 1990s due in part to increased reporting from study monitors, ethical review boards and research sponsors and due to improvements in convenience and anonymity in filing complaints. During the past decade, however, the total number of complaints filed as a percentage of active investigational new drugs (INDs) has been falling from a peak of 6.6% in 2003 to 4.1% in 2011. At this time, the FDA receives an average of 257 complaints for PI non-compliance and fraud each year with protocol violations, data falsification and poor drug accountability the top reasons cited.

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—Timothy Denman

<table>
<thead>
<tr>
<th>Year</th>
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<th>Complaints as a Percentage of Active INDs</th>
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Source: Tufts CSDD

Figure 1. The rate of complaints for investigator non-compliance and fraud is falling.
FDA, Research Organizations Seek to Bolster Drug Submissions

One sign of a healthy biomedical research enterprise is steady growth in new drug applications (NDAs) submitted to the Food and Drug Administration. There are signs of trouble, however, in the latest announcement of user fees for 2014 authorized by the Prescription Drug User Fee Act (PDUFA). FDA is increasing fees paid by pharma and biotech firms, as it has done steadily over the last 20 years. A key reason is that the agency calculates that it will receive only 116 submissions in 2014, slightly lower than the 122 applications filed in 2012. And because the agency has to collect a certain amount in fees each year, fewer applications means that each sponsor pays a little more.

Thus it will cost $2.2 million to submit an NDA or biologics license application (BLA) for agency review, according to a Federal Register notice published on August 2, 2013. A biosimilar application that carries clinical data will be just as pricey, while an efficacy supplement with clinical data to support a new indication or expanded labeling will cost $1 million. And although a $2 million application fee is relatively inconsequential for a large pharma company that spends billions on clinical trials and product development, it may be considerable for small firms with limited resources.

FDA sets its overall fee revenue target based on a “workload adjuster” that reflects inflation and the increased complexity of the drug review process. In addition to some 115-130 NDAs and BLAs filed each year, FDA receives nearly 7,000 commercial INDs, 140 efficacy supplements, and about 2,500 manufacturing supplements, according to the user-fee announcement. Sponsors will pay a total of $252 million in application fees, as well as equal amounts for FDA oversight of manufacturing establishments and marketed pharmaceutical products.

The drop in anticipated NDAs may reflect the squeeze on pharma investment in R&D and an ever-longer and more costly drug development process. FDA is on track to approve nearly as many new molecular entities (NMEs) as the near-record 45 in 2012, but those gains could halt in future years if applications diminish.

A more positive view of the approvals-and-innovative issue is to distinguish truly important NMEs—“first-in-class” and “advance-in-class” medicines that account for a growing proportion of new drugs—from “addition-to-class” drugs that are declining, say FDA analysts (http://bit.ly/14Z5OY). A rising number of advanced new therapies are coming to market, according to this new look at application approval rates, which counters concerns about total approvals remaining static.

Everyone would be a winner, moreover, if pharma and biotech companies filed more high quality applications. That would boost the approval rate despite fewer initial submissions.

**Streamlining studies**

One strategy for increasing the productivity of biopharma R&D is to develop a more robust clinical trial infrastructure that taps into health information more effectively, says Janet Woodcock, Director of the Center for Drug Evaluation and Research. She would like to see more ongoing clinical trials that utilize standardized methodologies to rapidly screen candidate compounds for signs of efficacy. “Let’s not reinvent the wheel with every trial,” she said at a July conference sponsored by the Brookings Institution. She noted that a “network of data sources” linked by common protocols and standards could greatly compress the clinical testing process.

Similarly, the National Institutes of Health aims to reduce the high failure rate of clinical trials through a target validation consortium, starting with pilot studies for Alzheimer’s disease, diabetes, rheumatoid arthritis, and schizophrenia. The Patient-Centered Outcomes Research Institute (PCORI) also is taking steps to improve the conduct of clinical outcomes research through its National Patient-Centered Clinical Research Network. The program will consist of some 25 research networks formed by academia, research organizations, and patient groups, each able to tap into health data for over 1 million individuals, explained PCORI Chief Science Officer Bryan Luce at the Brookings conference. He acknowledged challenges, such as devising more efficient oversight by institutional review boards, but predicted that the program will create “a dynamically linked clinical research network” able to test hypotheses and conduct adaptive studies, Bayesian trials, and observational studies.

By providing data from real-world patients in usual care settings, the PCORI research network appears likely to support industry post-marketing studies, as opposed to randomized trials for investigational medical products. The program also could help identify and recruit patients for experimental studies, encourage use of patient-reported outcomes, indicate to sponsors why certain patients don’t respond to treatments, and what endpoints are important. Key issues are how PCORI develops the governance and structure of the research networks, as well as who has access to the data.

—Jill Wechsler

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Only Small Steps Toward European Data Transparency

Industry organizations weigh in on the transparency debate.

Weary followers of the European data transparency debate will derive no comfort from the responses to the latest efforts to steer a middle path between indefensible secrecy and excessive disclosure. In late July, the European drug industry agreed on its long-awaited and carefully-worded position on the release of clinical trial data. But within days, leading figures in the key constituencies of academia, patient groups, and healthcare campaigners had issued statements ranging from the cautious to the downright dismissive. For Health Action International (HAI), the industry proposals “fall woefully short.” For the European Patient Forum (EPF), no limitation is acceptable on publication of results. And the scholarly assessment of the European Organization for Research and Treatment of Cancer (EORTC) of the pros and the cons of the industry approach concluded with an expression of regret.

What the European Federation of Pharmaceutical Industries and Associations (EFPIA) has offered—in conjunction with its US counterpart, the Pharmaceutical Research and Manufacturers of America (PhRMA)—is a series of “joint principles for responsible clinical trial data sharing.” They say these commitments “will dramatically increase the amount of information available to researchers, patients, and members of the public.”

Notably, companies will share clinical trial data at patient level and study level “with qualified scientific and medical researchers.” The same facility will be offered for clinical trial data, full clinical study reports, and protocols from clinical trials. But there are some qualifications and conditions. It concerns only trials in patients “for medicines approved in the United States and the European Union.” Data will be shared only “upon request.” The data access will be “subject to terms necessary to protect patient privacy and confidential commercial information.”

As part of this proclamation, biopharmaceutical companies have also reaffirmed “their commitment to publish clinical trial results regardless of the outcome.” According to EFPIA, what this translates into is that “as a minimum,” results will be “submitted for publication” from all Phase III clinical trials “and clinical trial results of significant medical importance.” The industry claims the principles will “enhance research and scientific knowledge, advance patient care, and improve public health.”

Interesting, but...

Françoise Meunier, director general of EORTC, said the industry proposals are “very interesting”—adding, “but, as you know, the devil is in the detail.” EORTC welcomed the initiative as it would “guarantee some minimal level of access to trial results and data on a more global level, and not only for trials run or submitted as part of a registration dossier in the European Union.” This is, it believes, an improvement on the policy of the European Medicines Agency (EMA) or EU regulations—even though its application is not worldwide.

Other features which EORTC welcomes include the apparent “willingness to increase CT data transparency from the industry,” and the recognition of “the important contribution of independent academic partners and the need to share information with them.” It considers it important that industry “clearly engages to make trial results public (in the form of a synopsis of the clinical study report), whether they be positive or negative, and including in the case where development programs are discontinued.”

There is also praise for the industry intention to allow independent review boards to review applications for access to data, and for the “high degree of transparency on the precise procedures that will apply.” This is “consistent with the EORTC approach to data sharing,” which Meunier contrasts with the EMA position, where no plans exist to make any assessment of the professional skills or proposed methodology of those seeking data access.

EORTC regrets

Deficiencies that EORTC identifies include the limitation to Phase III trials only in the industry engagement for publication of results. “More and more drugs, at least in oncology, are getting conditional approvals and being prescribed based on Phase II trial results,” EORTC points out, recommending an extension of this minimum...
engagement to cover Phase II trials as well, at least if the drug received provisional or definitive approval without Phase III data. Similarly, if drug development was discontinued before any Phase III could be run, these results should be shared too. EORTC wants a clearer commitment to publication of results for all clinical trials, irrespective of where they are run.

It also foresees obstacles in the nature of the scientific review committees that industry envisages for handling data sharing requests. Since these are to be set up at each company, smaller firms may find it a challenge, and researchers may need to contact many companies and undergo multiple reviews for a single project—notably in the case of meta-analyses. Instead, EORTC suggests that EFPIA puts in place a central review committee (at least for oncology) that companies could use on a voluntary basis, thus simplifying the tasks.

**Patient views**

The comments from Nicola Bedlington, Executive Director of the European Patients’ Forum, are shorter, and more direct. “Industry’s new overarching commitments on transparency are an important step,” she said. “But it is a much longer journey.” EPF remains firm on its standpoint: “We continue to call for the publication of all results of all clinical trials, be they industry or publicly funded, in an EU database with appropriate access for researchers and the public. Results should be made available in a timely manner after the end of the trial, regardless of the outcomes.”

**Woefully short**

HAI Europe has urged the drug industry to “truly commit to clinical trial data transparency.” And while it “welcomes any initiative that grants increased access to clinical trial data,” the commitments made by EFPIA and PhRMA “fall woefully short of the data transparency that is needed.” HAI questions the industry’s “overall commitment to transparency,” because “while they claim to support greater access” to clinical trial data, “they actually do the opposite,” it says, citing a recently-leaked industry briefing paper that was widely seen by industry critics as proof of industry opposition to greater data transparency.

From the point of view of HAI, mandatory public disclosure of all clinical trial data is important to minimize the risks that industry will practice selective reporting of trial results, leading to an overestimation of the benefits of medicines and an underestimation of the risks, and posing a significant threat to public health. Accordingly, the industry proposal to make only the synopsis of clinical study reports available, after marketing authorization has been granted, is inadequate.
"Disclosing only synopses of clinical study reports will not solve the prevailing dangerous practices of reporting bias and misuse of data by the pharmaceutical industry," according to Ancella Santos of HAI. It is crucial that the full clinical study report, including raw data, is available in a publicly accessible database, so as to ensure independent reviews of the safety and efficacy of medicines and to enable informed decision-making by healthcare professionals and consumers, she says.

In addition, the industry’s extensive list of restrictive conditions raises “serious doubts on whether the commitments put forward will in practice increase the set of publicly available clinical trial data.” In particular, HAI is alert to the risk that the definition of who may be granted data access “potentially excludes independent review by any other qualified experts including public health organizations.”

**Industry concerns**

Industry has attempted to ward off accusations of undue secrecy by spelling out its reasons for seeking some control on access. Although “companies routinely publish their clinical research,” companies will provide access to patient-level data and other clinical trial information “consistent with the principle of safeguarding patient privacy.” In addition, “where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.”

The qualification process for data requestors is explained at length by the industry. They will be “required to submit a research proposal to document the legitimacy of the research question and the qualifications of the requestor.” The evaluation will take account of “any potential conflicts of interest, including potential competitive use of the data.” And “researchers must agree not to transfer the shared data or information to parties not identified in the research proposal, use the data for purposes not contained in the research proposal, or seek to re-identify research participants.”

“In a sustainable research ecosystem, companies must be certain that their proprietary information will remain secure from disclosure to competitors,” the industry statement insists. That is why access will be given to “confidential commercial information—which could be used to help gain approval of a competing medicine—only for legitimate scientific and medical research.” These data sharing principles “are not intended to allow freeriding,” industry states unambiguously. “It would be appropriate for companies to refuse to share proprietary information with their competitors.”

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Third-Party Vendor Management

Considerations for third-party management in a risk-focused environment.

In the past, sponsors have experienced mixed levels of success allowing CROs to take full responsibility for ancillary, or sub-contracted, providers on a project. Yet, in a fully outsourced model, sponsors could theoretically maximize efficiency by giving CROs the freedom to select and manage sub-contracted providers. Linking Leaders Roundtable members have taken various approaches involving the following considerations, among others, in their decision making process:

Oversight. Sponsors continue to struggle with the risks and benefits of transferring the burden of managing third-party vendors to their CRO partners versus maintaining tight control. Some feel the lack of direct management can lead to negative implications to quality, cost, and speed. The root of this belief seemingly lies in perceptions that CROs are less committed than sponsors to oversight, and that issues tend to be minimized or escalation delayed while the CRO works to fix them. This can lead to feelings of mistrust between partners. However, lack of complete control is a challenge for sponsors because while they can delegate responsibility, the sponsor ultimately holds all the risk. Even if the sponsor delegates vendor management to the CRO, in the end, the sponsor is still responsible for its regulatory obligations. Many times a sponsor will pay a CRO to manage vendors and allocate internal staff to oversee both the CRO and sub-contractor; this practice duplicates efforts and therefore increases costs. Further compounding inefficiency, CROs with control over third-party delivery may still sometimes need to engage the sponsor regarding additional authorizations, resulting in the sponsor being involved in the very activities they have delegated to the CRO. Finally, accountability for delivery of services is often unclear; consequently, quality and/or delivery issues usually result in finger pointing and a corresponding increase in overall risk (higher costs, operational delays, damaged reputations, etc.) and a general degradation of the relationship.

Cost. In addition to oversight and potential duplication of efforts, spend is a key consideration when deciding whether the sponsor or the CRO should manage third-party providers. Issues cited by sponsors include the possibility of spend becoming less transparent when CROs manage third parties, and the sense that CROs do not negotiate in the best interests of the sponsor, especially as most sub-contractors are treated as pass-through costs by CROs. Cost transparency is of concern because the incremental cost to manage sub-contractors may get folded into other project management related activities, leaving sponsors with no real way to determine if the CRO is managing efficiently. Finally, and specifically when the delegation of responsibilities and accountabilities is not clear, any change to the initial assumptions underlying the costs for sub-contractor management and delivery causes sponsors to worry that the volume of change orders will increase when a CRO manages third-party providers.

Best-in-class providers. A sponsor may decide to outsource to a third party with specialized/technical expertise. In such cases, there may not be an in-house resource who truly understands the infrastructure end to end (either at the sponsor or at the CRO), so it may be difficult to accurately ascertain the level of quality received. While many CROs are capable of performing a wide variety of services (e.g., lab work, IVRS, ECGs, etc.) within their own company, and are able to offer large system efficiencies and better pricing, a potential conflict of interest could arise if the CRO is asked to manage another vendor providing services that the CRO also provides. There are, however, several CROs who routinely work with other CROs to deliver services to sponsors which have firewalls between these divisions to reduce potential conflicts of interest. Finally, some sponsors may question how much of the CRO’s business is actually awarded to a third-party vendor and whether they will be competing with other sponsors for time and resources because the loyalty is to the CRO rather than to the sponsor.

Rikki Bouchard, President and CEO of R.H. Bouchard and Associates, presented results from her recent industry-wide survey on business aspects of dealing with a CRO and things that could make it the “CRO of Choice” for a sponsor. One of 11 major categories surveyed focused on third-party vendor management, with some of the findings illustrated in Tables 1 and 2.

As far as the potential benefits are concerned, sponsor roundtable members acknowledge that allowing their CROs to manage third-party vendors enables them to assign fewer internal resources to a study. Particularly at smaller sponsor companies, the lack of...
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internal infrastructure and resources (headcount) to manage third-party vendors makes this a necessity. In a full-service outsourcing model, the CRO may also be in a better position to coordinate and manage service requirements and logistics, thus easing the burden on the sponsor. Allowing CROs to centrally manage more elements of a study may also give them more control over time/cost/quality, resulting in efficiencies. A CRO may have more experience working with a wide variety of vendors and, therefore, be better equipped to select qualified vendors for the study. The CRO may have greater leverage with the third-party vendor (due to a greater volume contract or a more strategic relationship) that would put them in a better position to influence resources to satisfy a critical need. One CRO roundtable representative indicated that some CROs are establishing internal groups specifically for the purpose of selecting, contracting, and managing third-party providers.

At some organizations, sponsors hold all contracts but empower the CRO to oversee and manage the vendors. More often than not, however, third-party vendors prefer to interact directly with the decision maker (sponsor) for several reasons. For one, they believe they can service the sponsor better, with more clarity and understanding of performance expectations, potentially allowing for a more strategic book of business. In addition, the ability to standardize or replicate activities could enable the third-party vendors to provide more competitive rates given the ability to leverage total spend across study programs. Direct contact with the sponsor also facilitates relationship building and eliminates the middleman (CRO) if problems should arise. Also, in a competitive environment, many third-party providers do not want to share proprietary pricing with CROs that might offer the same services.

The consensus of most roundtable members is that sponsors would like to turn more of the responsibility for managing third parties over to the CROs, allowing for workload to be shifted from internal resources to outsourced providers. Ideally, these providers would be operationally invisible, but the sponsor would be aware of the process for selection, pricing, and contracting. However, there needs to be some assurance that the CRO is using best-in-class providers and managing them proactively. If there are rebates based on volume spend, sponsors would like to see this saving passed on. CROs prefer to work with third parties they themselves have qualified. “Unknown” vendors could become an issue if the CRO is responsible for their performance. Even if the sponsor has assessed the vendor (and provides a copy of their audit report), it is recommended that CROs do their own due diligence. As noted above, many CROs have, or are establishing, their own rigorous processes for third party/subcontracted services; so, when largely unknown providers are proposed by sponsors, CROs would then have the mechanism to qualify, contract with, and oversee delivery to help ensure performance.

Executives are left wondering if there is any one answer when it comes to third-party management and how to support their CROs who manage subcontractors so that potential issues are proactively addressed and effective oversight is enabled. Communication and transparency are key, starting with all parties gathering around the table at kick-off meetings, planning for issue escalation, and partnering to mitigate issues. It is also helpful for the CRO to have the full development picture so that concerns around timelines are treated with the same sensitivity as they would within the sponsor organization.
Implementing a new approach to study design: what can I expect?

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EVENT OVERVIEW:
Sponsors are increasingly exploring process changes, such as innovative protocol review meetings along with the adoption of technology that provides standards based structured protocol design, in an attempt to make the drug development process more efficient and cost effective. These new approaches to study design, provide a clearer line of sight to the relationship between the objectives, endpoints, and procedures of that study. The benefits include reductions in costly protocol amendments, complexity, patient burden, and more efficient study builds during study execution.

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Medidata Solutions

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Vical

Ian Shafer
Senior Manager
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Moderator
Lisa Henderson
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Ensuring the quality of a clinical trial in today’s challenging drug development climate hinges on several important elements, perhaps none more crucial than the start-up phase, where much of the groundwork for a product development program is built. Achieving predictability in study start-up has become a critical goal within the clinical research timeline. Until recent years, activities associated with study start-up—which include site identification and feasibility, negotiations of contracts and budgets, planning for patient recruitment, managing/ tracking regulatory documents, and drug accountability—were largely executed through numerous and often cumbersome manual processes. This would frequently lead to inefficiencies in study timelines and cost. Today, with the advancement of electronic, real-time document collection and data reporting systems, along with increased efforts by biopharmaceutical companies and their contract research organization (CRO) partners to align these technologies with specialized personnel in areas such as critical path project management (CPM) and resource centralization, strides have been made in streamlining study start-up and reducing trial initiation times.

Despite this progress, there remains a strong need for the industry to evolve start-up approaches to the next level. Pursuits in data collection and analysis must now focus on the underlying dimensions unique to an individual country or site being targeted for clinical research. This is particularly important amid the rapid globalization of drug development, where access to the right intelligence during study start-up is critical.

Intelligence has evolved to go beyond the typical site-level information. It is now captured at the country level, which allows for better feasibility outcomes. Intelligence also now incorporates the regulatory environment risks, the timelines for site contracting, and budget negotiation, as well as submissions, and even time to schedule critical path visits, such as pre-study and site initiation visits. In addition, site intelligence consists of enrollment capabilities and the site’s ability to meet enrollment goals. As data integration of country and site performance improves, so will the selection of the best sites available to complete the project in the shortest timeframe. The increasing integration of investigator databases with companies’ already proven processes should aid these efforts.

An additional consideration involved in gathering intelligence is understanding and gathering data around the more complex clinical trials and creating relationship models across the therapeutic areas. This will result in a higher level of data integration. Such integration, however, will be difficult to achieve if best practices in study start-up are not adequately implemented. To that end, sponsors and CROs must find innovative ways to operationalize start-up activities through technology.

Challenged from get-go
While recent studies have reported improved trends, sponsors and CROs continue to experience significant challenges in meeting overall clinical trial timeline demands. According to Cutting Edge Information, 72% of studies run more than one month
behind schedule. Such delays can impact the bottom line, with sponsors standing to lose between $600,000 and $8 million for each day that a trial delays a product’s development and launch. Challenges in patient recruitment and retention are considered the major cause of drug development delays, but start-up activities are key factors as well, particularly issues around site contract and budget negotiations and approval. This may be a result of increased costs of clinical trials at the site, a more competitive environment, or the result of financial pressures on sponsors to keep investigator payments low. The Tufts Center for the Study of Drug Development finds that while the majority of clinical trials globally meet their patient enrollment goals, sponsors and CROs typically need to nearly double their original timelines to reach those targets. Nevertheless, Tufts reports that 89% of clinical studies meet enrollment expectations, with site activation rates reflecting success with study start-up in particular.

Historically, the study start-up phase has been viewed as a labor intensive, costly, and time-consuming component of the clinical trial process. Today, sites must perform a number of specific activities related to documents, submissions, contracts, and visit schedules across multiple studies with multiple sponsors. These documents include site feasibility survey forms, protocols, investigator brochures, site contracts, budget worksheets, patient recruitment plans, informed consent forms, and advertising materials. Ensuring that the most recent versions of these documents are used can be challenging if there are multiple versions and amendments. Heavy paper-based processes have long burdened efforts in study start-up. For instance, Form 1572, which each investigator participating in a trial must complete, was identified as the single most redundant paper received by the U.S. Food and Drug Administration (FDA). Manually processing each 1572 could result in weeks of elapsed time per investigator. Devoting resources to the manual routing and tracking of these forms also frequently requires the use of valuable resources that could be allocated to other more critical tasks.

Several inefficiencies and limitations continue to threaten the data-collection process during study start-up. For many global trials, there is little standardization for what data is collected, and there are typically multiple places where the information is stored. There is significant need for sites to be able to provide and update their information to a single source rather than multiple sponsor and CRO databases, all with differing criteria. Also impeding efforts in this area is a lack of industry standards regarding the terms or milestones to measure. Though initiatives around integration have increased, sponsors largely feature standalone databases that typically do not feed
information into vendor workflow systems, making it difficult for clinical teams to measure the data. Instead, CROs usually are required to mine the database and pull out information. This can present challenges because study start-up does not just focus on metrics around what sites have conducted a particular project and how many patients they enrolled, but also involves timelines related to regulatory activities and site contracting.

Another challenge for outsourcing providers, in particular during study start-up, is the management of resources in cases where there is no global source of information regarding a development program and the window from a request for proposal to award of a study to a CRO can be as short as one month. When assigning staff, CROs must be able to predict the number of personnel and resources that will be needed within each country to assist with language and cultural barriers, as well as how to distribute and utilize those resources as efficiently as possible. With start-up staff at these organizations routinely moving in and out of projects, CROs need the necessary visibility to plan across their overall resourcing strategy. It is crucial, therefore, that technology used in study start-up be built in to allow for more proactive and effective resource planning at the country level.

Similarly, better strategies are needed to reduce any project downtime often associated with study start-up. Sponsors and CROs have traditionally functioned as stand-alone activities, which inevitably creates inefficient “handoffs” between the various steps in the process. This can lead to gaps in time between activities that may range from hours to days, thus slowing down overall clinical trial timelines and potentially compromising study budgets. The use of technologies allow for the seamless sharing and visibility of documents and information in real-time throughout the world that streamlines any necessary handoffs. Technologies that use workflow management systems, alerts, document collection, version control, and reporting eliminate the number of handoffs, errors, and downtime along the start-up continuum, and produce critical efficiencies in CPM and workflow design.

In the United States, activities involving local institutional review boards (IRBs) have traditionally challenged efforts to simplify study start-up. Typically, multicenter clinical trials a site can use a central IRB or a local IRB. Central IRBs review the protocol for multiple sites. Sites that are required to use a local IRB—usually academic and institutional centers—appear to have a less efficient review process and require more time to gain approval. Each site’s local IRB conducts a full review of a multicenter protocol, and this process, repeated at each site, produces very similar outcomes that add significant delays to the start-up phase.

With multicenter studies becoming increasingly more common, some have questioned whether local IRB review actually enhances the goal of protecting patients. A recent study contends that multiple reviews and differences in informed consent forms may result in differences in the way patients are treated from site to site, with no ethical justification. The report notes that the FDA and other US agencies have encouraged the use of a central IRB to improve the efficiency of trials with multiple sites, though research institutions differ in their willingness to defer to centralized IRB review.

Studies have shown that the use of a central IRB results in a site’s approval an average of 27 days sooner than when using a local IRB. With more pressure being placed on shortening the timeframe to start studies, site selection is becoming more competitive. Sites utilizing local IRBs can be at a greater disadvantage in cases of competitive enrollment. Central IRB sites have more resources to achieve optimal quality and performance goals as well as ensure appropriate oversight to adhere to regulatory guidelines. There has been a large trend globally for the centralization of IRBs and ethics committees. This trend will also lead to better oversight from regulatory agencies and will increase consistency and protections for study participants.

There are several therapeutic areas that pose particular challenges during the clinical trial start-up phase. For instance, in oncology, with the emergence of molecular-targeted therapy, the complexity of study protocols has increased, allowing for the inclusion of patients with a wide range of tumor types that share a common genetic mutation. Including diverse cancer disease types with a shared genetic mutation can lead to additional challenges for study start-up and implementation.

Trials that target central nervous system disorders may present the greatest challenge to start-up efforts. Studies in this area typically feature very complex protocols, and are largely conducted in institutional environments that utilize local IRBs or ethics committees. With disease-modifying treatments desperately sought for cognitive impairments such as Alzheimer’s disease and Parkinson’s disease, research institutions that specialize in CNS disorders are highly tapped for clinical trials. However, whether state run or private, these institutions generally encounter numerous challenges when initiating a study, particularly around site contracting, specialized institutional review committees, and addressing ethics committee and regulatory requirements.

**Strategies evolve**

Amid the growing challenges in study start-up, strategies in this area are increasingly emphasizing workflow management as opposed to simply the tracking of data. This approach allows study teams to better manage key start-up steps through process improvement techniques such as CPM and Lean Six Sigma methodologies. The goal is to create global visibility and foster better communication and understanding around issues such as when sites are available for pre-study visits, for example, or when they are qualified after pre-study visits, and then being able to perform those project handoffs on a global and much more visible basis. Workflow management also enables greater focus on certain start-up activities that may be outside a sponsor’s or CRO’s specific functional areas. Drug shipment to sites,
for example, will be easier to manage as workflow systems continue to evolve and predictability of site activation is enhanced. Staffing of clinical research associates can benefit from these approaches as well.

Companies today are building their databases to allow sponsors and CROs to see more clearly into the future based on past project experience. Using this information to evaluate new protocols and products according to their overall design and composition can help identify risks or trouble spots that may occur along the same path. However, simply basing projected timelines on general comparisons with past trials in the same phase and indication is not sufficient. Depending on the level of complexity, there are several aspects of study start-up that require in-depth evaluation to attain predictability in start-up. Protocol design evaluated against the regulatory environment, patient population, and standard of care allows for the identification of risks that can potentially be mitigated through better selection of countries and changes to submission documentation or approach with the regulatory agencies to gain advice in advance of submission. Investigational products, concomitant medications, supplies, and laboratory exports also need to be reviewed against the regulatory environment to ensure the ability to import and export needed clinical trial products, as well as samples for evaluations at centralized laboratories. It is critical, therefore, that study teams are able to enter multiple unique parameters of a new study into the intelligence databases upfront to create plans that increase the likelihood of predictability around timelines.

During the clinical trial, measuring against performance is key to ensuring baseline timelines and plans are managed appropriately and variability is understood. Study tracking of key deliverables should be performed against a baseline plan that establishes realistic end-to-end goals at the beginning of the project. If circumstances arise that change the timeline, then a projection should be created, however, the original plan should always remain as the baseline. Staying as close as possible to the baseline plan will ensure that the appropriate data is available when measuring predictability. If there is a delay that is inevitably part of the start-up process, this approach will allow for the gathering of information that will lead to a quicker mitigation strategy.

Activities related to site identification and feasibility can benefit significantly from improved data strategies. Identifying high performing investigators and sites is essential for research outcomes because the activity directly correlates with quicker patient enrollment, the attainment of overall enrollment goals, higher quality data, fewer queries, and better subject retention. Poor selection of trial sites, however, remains a problem in the industry and reportedly increases the cost of clinical trials by at least 2%. Poor site selection is largely attributed to the lack of knowledge of active and relevant clinical investigators. In addition, database-driven site selection is still a relatively new option for the industry, as many sponsors con-
TRIAL DESIGN

tinue to rely heavily on their relationships with previously-used sites to find suitable investigators.9

Typically, when recruiting sites, sponsors and CROs first identify which regions the targeted patient population is more commonly located. Next, they determine whether the protocol is appropriate for those particular regions. Access to regulatory intelligence databases can help improve the success of these decisions by applying key information to country and site feasibility assessments. Those companies able to combine information around timelines and metrics data with robust regulatory intelligence will be able to establish a strong foundational knowledge when exploring geographies to conduct trials. That should, in turn, help expand and refine their network of qualified sites and investigators.

The practice of enrollment modeling can also help improve study start-up efficiency. This method allows study teams to estimate the time needed to recruit the required number of enrolled patients using a set number of sites. Enrollment modeling has application throughout a trial, providing a plan to measure enrollment progress as the study advances. Technology in this area enables study teams to view in parallel enrollment data and intelligence regarding specific protocols, countries, and sites from an end-to-end perspective. It is important that all systems built into a clinical development program feed into the specific enrollment modeling technology being used.

Technology push

Global reporting systems and technologies in clinical development have advanced considerably over the past decade, largely shifting from the tedious exercise of compiling Excel spreadsheets to technologies that allow for more real-time data and reporting. Systems today, for example, enable queries from ethical committees and regulators to sites in various countries to be shared globally in real-time. The process of communicating with investigators is becoming increasingly digital, although site adoption of web-based tools for clinical document exchange remains slow. A global survey conducted by CenterWatch in 2011 found that 73% of sites were still using traditional methods of e-mail, fax, and courier as a primary tool for exchanging clinical trial documents.10 Nevertheless, the majority of investigators, even those in developing regions, have access to smartphones, tablets, and other mobile devices. This reality puts further onus on sponsors and CROs to consider sites’ needs accordingly. That could mean making sure that investigator questionnaires, for instance, can be distributed electronically, completed on a handheld device, and signed with an electronic signature. Providing investigators routine, pre-populated documents that can be quickly completed via mobile would help speed up the overall start-up process. As technology improves, the clinical trial environment will need to keep up with the demands to manage start-up in order to remain competitive and reduce timelines.

Online clinical document exchange portals are being used to simplify the task of tracking study start-up activities for multiple sites. These portals can enhance visibility into the status of a site’s progress through reports generated directly from the system. Streamlined communication with sites potentially allows sponsors and CROs to track and collaborate on operational data in a more transparent, regulatory-compliant, and user-friendly manner. In addition, smart workflow technologies make it easier for study teams to provide real-time status updates to management that it can use to find process bottlenecks and optimize resources. It is important to be mindful, however, that adoption of digital portal systems is not without challenge. For sites already overburdened with work from multiple sponsors with their own systems for start-up, there may be reluctance to learn a new technology. In addition, adopting a new system requires the creation of new SOPs and a commitment to additional staff training. For sponsors and CROs, there are issues to consider such as cost of the initial investment and the potential return on investment.11

Because study start-up activities are repetitive and consistent across all clinical trials, there is increased recognition that implementing technologies that deliver process efficiencies can generate valuable time and cost savings. This realization has led to more industry collaboration around leveraging such efficiencies. For example, in September 2012, 10 big pharma companies formed a nonprofit, called TransCelerate BioPharma Inc., which is developing shared industry solutions to simplify and accelerate drug development. The collaboration has launched five pre-competitive initiatives, including a program focused on speeding up study start-up timelines through the development of standard criteria for mutual recognition of good clinical practice (GCP) training and site qualification. The program is also exploring a standard process for information requests related to site qualification, including investigator CVs, profiles, and site-specific profile information. Another TransCelerate initiative involves a cross-industry investigator portal that offers a central point of access and single sign-on for investigators and site staff.12 Also recently, three biopharmaceutical companies formed a collaboration to launch a shared investigator database aimed at eliminating certain redundant procedures in study start-up. The database contains such information as infrastructure details, GCP training records, and site capabilities.13

Conclusion

Although notable advances have been made in the way study start-up activities are conducted, there remains much work to be done if true efficiencies are to be gained in clinical trial performance to increase predictability in site start-up. The emergence of new approaches to streamline burdensome and time-consuming start-up procedures offer promise, but with still uneven adoption of digital document management and integrated data systems, challenges in predicting start-up timelines and identifying potential holdups will continue. Therefore, the need for companies to compile intelligence and drill deeper...
into the evaluation of protocols and the regulatory environment when projecting site activation is crucial.

References

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Electronic Data Capture in Clinical Trials

Sunil Shewale and Sameer Parekh

Does the emerging world still lag behind in EDC adoption?

In early 1990s, the clinical research industry was more dependent upon paper-based systems for collection of patient data, leading to increased cost and time for trial completion. With the growth of the clinical research industry and its extension into emerging countries, many clinical research organizations (CROs) are approaching global electronic data capture (EDC) in an effort to improve the competence and accuracy of patient data collection methods. Although there are several advantages to move on to a paperless system, there are several key factors that impede the success of EDC systems. Many organizations are still at the early development stage and real tangible benefits have yet to be realized with eClinical systems.

The pharmaceutical industry is at an important crossroads in medical innovation, and the competitive pressures of today's marketplace are forcing the industry to seek ways of reducing drug development times and increasing productivity. Setting up the businesses in emerging countries like India and China and curbing the clinical trial lifecycle by collecting quality data more quickly and accelerating the processing of available data are just a few solutions. This has led to the growth of EDC, which has its origins in software called Remote Data Entry (RDE) that surfaced in the life sciences market in the late 1980s and early 1990s.

Today nearly half of all new clinical trials are initiated using EDC. Industry analysis predicts that investments in EDC solutions will increase at a 14.7% compound annual growth rate and total more than $3.1 billion. Similarly, the integration of EDC software with other types of software in the eClinical spectrum (randomization, supply management, adverse event reporting, coding, submissions, etc.) systems is increasingly feasible and could prove beneficial.

However, the use of EDC systems for clinical trials in developing regions has been affected by a number of practical, technical, and technological issues, which are not limited to the natural workflow of healthcare professionals, costing, limited IT infrastructure, inadequate training, language barriers, etc. Interim reports from a recent survey conducted by the eClinical Forum show that the use of paper case report forms (CRFs) is rising even as EDC adoption is increasing. Thus, drug developers must seize the opportunities and use advanced tools to find more efficient and scalable ways to use EDC systems in emergent markets.

Natural workflow of healthcare professionals

Although technology is in the forefront of drug development, many doctors working in rising countries prefer things the old-fashioned way. For example, Indian clinicians find that EDC is impractical, often hindering their work because they are used to keeping notes on paper. Similarly, many healthcare professionals follow the practice of capturing study data by hand while in front of a patient. Such aversion to keyboard-
based entry during patient contact is a common practice, not just in emerging regions. In one survey, almost 60% of healthcare professionals said they thought it was never appropriate to enter data into an EDC system in front of a patient, and 17% said it was appropriate only in rare circumstances. The ClinPage report mentioned above also noted that, in 2001 and in 2009 when the survey was conducted, 16% and 26% of respondents respectively said study data was initially entered from a paper CRF into an EDC system. Such type of workflow affects the EDC systems naturally, which may not have the trial data until 48 hours to a week—or longer—after it is written down or collected in some other system, despite contractual obligations to provide the data entry within shorter time windows.

For the reticent then, it appears there is a need to accommodate the pen-on-paper-based workflow and integrate it with the data repository and management function of an EDC. In recent years several technologies have been developed that could serve as a good complement for EDC systems. These are point-of-contact data collection systems using devices such as the digital pen, tablet PCs, and more. These devices allow the user to input data using a natural pen-based workflow.

Cost a major concern
Although the implementation of an EDC system looks to be an upward path for the foreseeable future of trials in emerging regions, much of the nature and intent of the activity is changing below the surface. Use of EDC for trials in such regions is a relatively new concept and has created the need to develop the system, training, time spent on problem resolution, etc., which has naturally increased cost. These functional difficulties that increase the expenditure are highlighted in Table 1. However, companies have reported that EDC has actually increased costs in some regions. Although the majority of western companies conducting trials in China use EDC, most Chinese companies do not. One of the main reasons for this is the cost of adopting EDC technology versus the low cost of Chinese labor. Companies that believe EDC implementation in developing countries saves money may use EDC for all in-house managed trials. In addition, without suitable incentives and technology, there is the likelihood that investigative sites won’t transfer data from paper records days or even weeks after the patient visit—thereby negating many of the potential benefits of EDC and adding more cost.

Although the cost savings for paper-based systems versus EDC has been well known, there is the parallel problem that paper-based methods are well-established in poor countries, and that these costs are no longer examined. However, to know the actual cost of any project, the real-time comparison of cost required for EDC and paper-based system is necessary.

Lack of technological infrastructure
Participation in global clinical trials requires an updated infrastructure and facilities. The lack of quality and IT infrastructure support for EDC is another area of concern for a number of countries. For example, between 10% and 14% of trial sites in China require computers be supplied compared to 1% and 2% of sites in the United States. The majority of trials in the West that use EDC rely heavily on Internet access—something that is not always available in India and other under-developed countries, particularly in remote areas.

Table 1. The various functional difficulty levels of EDC system.
areas. For instance, Internet access in Asia and Africa is less widespread than in the West (Figure 1). Another concern for companies is whether or not the EDC they choose will integrate with other eClinical products they are using such as clinical trial management systems, interactive voice or web response and electronic patient reported outcomes solutions. And while the CDISC data interchange makes interoperability between vendors products easier, most people in India use Excel spreadsheets or CSV files for the import of external data. Furthermore, affordability to build complex web-based solutions and consistency of Internet services in different regions are some of the major hurdles for use of EDC in India and other similar countries.

**Training**

As EDC is comparatively new to the clinical trial industry in emergent regions, healthcare professionals are not very well acquainted with it, and people may require appropriate training in operating the software. But, the emerging countries lack the number of available trainers for this purpose and those available are IT experts having limited knowledge about trial-specific medical parameters, which creates delays in operational activities.

Training to ensure an acceptable level of self-sufficiency is essential for an EDC trial. Training, either standard or custom, must be scheduled at convenient locations and conducted in the local language to ensure that all trial staff understand the application and are comfortable in the use of the technology. If the design of the trial necessitates a unique skill, custom courseware should be developed for that specific functionality.

**Study site issues**

Although, many global sponsors generally prefer to use EDC for data capturing in nascent countries, local study site issues can affect it. For example, many local sponsors and investigators in India are not ready to use EDC for trials, for them it is more complex. They often complain about some systems being too slow to use, unsuitable for use in a busy clinic environment, impossible to use to capture data with a patient in front of them, additional workload, and overall data-entry burden. Like other investigative sites, emerging countries generally have common site staff to handle different trials from different sponsors, with unique software packages for each.

Clinical trials in emerging regions span the healthcare delivery system from local or regional hospitals, to rural care. While working in rural areas, study sites usually suffer from multiple problems such as slow speed of Internet connection, non-availability of dial-up, difficulties in using LAN connection to access EDC websites and existing portability issues that affects data entry directly into the EDC. Wireless EDC systems have been extremely successful, with the technology showing much promise for running clinical trials in developing countries and areas that lack reliable Internet access. The best way to use fixed telephone lines and cellular phone networks to solve the problem, but the issue of EDC connectivity in regard to reliability remains.

**Language and cultural barriers**

Extension of clinical trials in emerging countries has been affected by language and cultural disparities such as lack of unifying translation standards, significant structural differences between languages, and vast linguistic and cultural differences among patients. Culture has a significant impact on the behavior and perception of individuals not only in each country, but also within a specific community. Thus a clear understanding of any cultural aspects that can interfere with the patient’s or investigative site staff’s comprehension is necessary. A clinical study conducted in various states of India may require knowing several communities including Hindi, Punjabi, Marathi, Malayalam, Telugu, Kannada, and Gujarati. To date, the majority of EDC systems are English-based and many languages into which materials must be translated are quite unrelated to English. As a result, identifying language equivalents can be particularly challenging. Chinese uses characters rather than letters and is composed of two separate character sets. Unlike English,
a single character typically represents multiple grammatical forms (for example treat, treating, and treatment). Thus, a sentence constructed in Chinese may be considerably different from the English one. Another example is that abbreviations do not exist in Chinese, and thus each word must be translated first into Chinese and then abbreviated.

Implementation of technical support in any given language and translation of user manuals, web-based interfaces, and automated materials for the collection of patient data, patient questionnaires, and patient diaries into required native languages can overcome the language barriers. Similarly, patient-generated or reported data requires a clear understanding of any cultural aspects that can interfere with patient comprehension. However, familiarity with the specific factors that affect the transmission of correct information, patient comprehension, and the accuracy of patient data is also essential. Thus it becomes very important to enlist the help of individuals who can make the difference and act as “cultural experts.”

Regulatory issues
Regulatory authorities in evolving countries need more comprehensive understanding of EDC and may require more time and support resources. For example, today India is considered a hub for clinical research and IT solutions, still the regulatory authority (DCGI) heavily relies on paper-based data. This may be because verification of data is necessary to confirm the participation of subjects and to detect omissions, transcription errors, alterations in data, or falsification of data, and when paper documents are available it can be performed easily.

Regulatory authorities need to be more updated to match with the existing technologies and international standards and develop a common approach for eSource documentation. FDA has set standards for electronic records (21 CFR Part 11) and also have prepared draft guidance for industry on capturing, using, and archiving eSource data in FDA-regulated clinical investigations in December 2010. Other regulators should take such initiative for successful adaptation of EDC in trials.

Privacy and data protection
Privacy and data protection is a worldwide issue for any type of electronic data and at times it can be difficult to maintain it while using an EDC system. Identification of trial patients can be possible from, for example, facial characteristics identified in a computed tomography scan. Similarly, the increasing affordability of genomic information, and its consequent incorporation into clinical trials, adds to the difficulty of ensuring privacy; it has been estimated that it may be possible to identify an individual from no more than 75 to 100 single-nucleotide polymorphisms. Although, Western companies have strong security systems for data protection, this issue still exists for them. Privacy and data protection requires strong laws, and India has recently passed the cybercrime law for protection from Internet hacking.

CRO perspective
Many CROs focusing on data management tools have business models in developing countries based on paper-based structure. Likewise, set-up of clinical trials, protocol writing, trial planning, design of case report forms, monitoring, etc., are reliant on the paper model. However, to address the challenges of the eClinical environment in these countries, CROs need to become eCROs, where technology drives process efficiencies.

In the current emerging market, very few CROs have an interactive voice response system and an interactive web response system in place for record tracking, and in-house EDC system design and development experts. They rely on other vendors for EDC technology; furthermore, not all vendors provide end-to-end services to support drug development, and others will not provide services like clinical data management, medical coding, etc. They are contingent on the client to take responsibility for these areas, either themselves or through a CRO. Translation services are cumbersome and lack the comfort level associated with support needs to be available in the site’s local time zone—having the help desk agent communicate with the clinician in his or her native language, both to secure the details of the incident as well as communicate the solution is ideal. In short, CROs are dependent on the service provider for EDC software, and larger CROs can have relationships with several vendors depending upon the study and requirement of the sponsor.

Identifying and categorizing potential solution providers, involving the right players, learning from experiences, narrowing the playing field, evaluating candidate solutions in a real-world setting, and ultimately selecting the right partner to meet the company’s needs may help for proper vendor selection but “one-size-fits-all” could be a key solution for better vendor management.

Real-world EDC verity
Everyone in contact with the EDC system has different needs, which raises the concerns and reduces the usability of an EDC system (Table 2). On the other hand, the number of data sources including standard laboratory data (hematology, biochemistry, and safety data), specialist laboratory data (biomarkers), echocardiogram (ECG) data,
Continuous follow-up may avoid complications. The procedure of upfront detailed definition of requirements and their considerations and met before using EDC systems. An investigator, and other trial participants, etc. Eventually it has to be ensured that regulatory requirements are thoroughly considered and met before using EDC systems. An upfront detailed definition of requirements and their continuous follow-up may avoid complications. The procedure of recording of source data in e-trials has to be defined for each site up front. Similarly, placing excellent service delivery at the heart of all innovation will ensure that any introduction of new technology will deliver value to the industry. Then emerging countries will also welcome the EDC and can undeniably articulate that the time to move to the EDC system for clinical trials has come.

**References**


**Editor’s note:** All opinions expressed herewith are those of the authors and do not reflect the views of their organization.

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**Table 2.** Common concerns to EDC adoption by stakeholder.

<table>
<thead>
<tr>
<th>STAKEHOLDER</th>
<th>CONCERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Site and Study Staff</td>
<td>• Required to enter data electronically</td>
</tr>
<tr>
<td></td>
<td>• Need training on the technology</td>
</tr>
<tr>
<td></td>
<td>• Need hardware provisioning</td>
</tr>
<tr>
<td></td>
<td>• Technical and operational difficulties</td>
</tr>
<tr>
<td></td>
<td>• Appointment of technical person</td>
</tr>
<tr>
<td></td>
<td>• Extra investment</td>
</tr>
<tr>
<td>Clinical Data Manager</td>
<td>• Job security or dissatisfaction</td>
</tr>
<tr>
<td></td>
<td>• Redevelopment of internal processes</td>
</tr>
<tr>
<td></td>
<td>• Limited application of personal and intellectual skills</td>
</tr>
<tr>
<td>Clinical Research Associates</td>
<td>• Often called on to provide investigator training</td>
</tr>
<tr>
<td></td>
<td>• Must act as discrepancy manager</td>
</tr>
<tr>
<td></td>
<td>• System difficulties resolution or management</td>
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</tbody>
</table>

Source: Sunil Shewale and Sameer Parekh

images from various types of medical scanning (computed tomography (CT) scans), positron emission tomography (PET) scans, etc., has dramatically increased in the last few years and are used along with CRFs. Acquiring, storing, transmitting, merging, validating, and checking all the associated data and metadata from these sources often reduces speed, requires more diverse systems, and causes quality issues.

**Conclusion**

The promise of increased efficiencies stemming from EDC has existed for years. However, use of EDC as a standard clinical trial tool in emerging countries is slower than expected; the prerequisite for this is the limited adoption of EDC with very little technological and technical support to adapt to future trends. With EDC, technology is not the solution, but the enabler. In order for any technology to be effective, it cannot be implemented without consideration of the context in which it will be used, the processes it will be used alongside, and the results required.

These deliberations include nationwide initiatives for implementation of health information structures; strict adherence to standards for data interoperability; software solutions based on open and public standards not on proprietary technology; changes in the attitudes of doctors and patients; intensive training to site before implementation of such a system; and better cooperation between patient, physician, investigator, and other trial participants, etc. Eventually it has to be ensured that regulatory requirements are thoroughly considered and met before using EDC systems. An upfront detailed definition of requirements and their continuous follow-up may avoid complications. The procedure of...
Timely patient recruitment is widely acknowledged to be the single most important aspect of successful clinical trials. Yet delays hamper almost 85% of all Phase II–IV clinical trials, bloating budgets and extending the waiting time before the public can take advantage of new medications that might improve or save countless lives. And since prescription drugs have a limited period of product exclusivity, shortening clinical trial times by just one month can generate as much as $40 million in additional sales revenue.

Several factors play a role in decelerating the patient recruitment process. Study protocols are becoming increasingly complex, adding more layers to the recruitment funnel. The shotgun targeting approach used in some recruitment strategies can be like searching for needles in a field of haystacks. Lack of awareness about trials is another stumbling block. One study of more than 1,000 US adults found that only one in three had even heard of clinical trials. In addition, public confidence and trust in clinical research have been steadily eroding for decades. Lastly, both the number and size of clinical trials are growing rapidly, creating an unmet demand for more and more patients, including many in diverse, difficult-to-reach populations.

In 2010, clinical study sponsors, investigators, and their partners spent more than $2.3 billion on patient recruitment, and such expenditures are growing 15% annually. Despite these efforts, two-thirds of investigator sites fail to meet the patient enrollment requirements for a given clinical trial, according to the Tufts Center for the Study of Drug Development.

Given these conditions, it’s no surprise that the clinical research industry is looking for new ideas. An innovative, patient-centric strategy showing considerable promise involves leveraging pharmacies as a recruitment channel. With their access to and personal knowledge of patients and their medications, pharmacists are uniquely qualified to add value to the targeting and overall effectiveness of patient recruitment initiatives.

Expanding role of pharmacists in healthcare

The pharmaceutical industry has dabbled with using pharmacists for patient recruitment since the mid-1990s. Most of these programs involved little more than notifying a pharmacy’s patients by letter that they might be eligible for a nearby clinical trial. Despite their modest scope and lack of patient follow-up, these programs demonstrated the potential value of leveraging pharmacists.

“We knew pharmacies were a great place to recruit. And from the perspective of sponsors and clinical research organizations, these early projects did quite well in cutting the time needed for targeting,” says Scott Ballenger, President of the Trial Acceleration Institute, who was involved in some of these early projects. “The retail chains, however, viewed them as more of a distraction to their pharmacists than as an opportunity. So when
It’s no problem to use prescription data to identify large numbers of patients with migraine headaches who use a triptan for treatment. But finding those who are newly diagnosed and have been on these medications for less than three weeks is considerably more difficult, requiring a more extensive, real-time review of potentially eligible patients’ prescription histories.

This was the challenge for a web-based observational study to help understand triptan utilization patterns and stability over time. The sponsor selected the McKesson StudyLink Program to identify, recruit, pre-screen, enroll, and compensate newly diagnosed migraine patients, who were eligible only if they were new to taking a triptan and had recently taken their triptan medication for the first time.

As the study’s sole recruitment source, StudyLink engaged 333 pharmacies through the McKesson Sponsored Clinical Services Network, a nationwide network of community pharmacies. The program identified potential candidates through prescription claims and demographic data. The participating pharmacists confirmed the claims data and verified that each patient was in fact triptan naive.

Patients were then sent a personalized letter from their pharmacists to inform them of their eligibility. The McKesson call center followed up and conducted patient outreach for pre-screening, education, and referrals to ensure that all patients met the strict protocol eligibility requirements. The call center team also added strategic value to the study by identifying patterns related to scripting and eligibility barriers and providing real-time feedback. The study sponsor subsequently submitted a protocol amendment to the IRB. Upon approval and implementation of these changes, the screening failure rate decreased from 86% to 67%.

StudyLink referred 221 patients into the study and 161 of them enrolled—a 73% success ratio. These results demonstrate that programs that leverage pharmacist-patient relationships to vet and validate data can effectively reach study candidates.

More information is available at http://www.mckesson-studylink.com/.
clinical trials and its wariness concerning the clinical trial profession. For example, a 2007 Harris Interactive poll found that more than four in 10 Americans distrust pharmaceutical and biotechnology companies. Pharmacists can help bridge the education gap and provide the antidote to rebuild trust.

Major international opinion polls indicate that pharmacists are one of the most trusted sources for health-related information. In Gallup’s annual honesty and ethics survey last year covering 21 professions, pharmacists ranked second only to nurses and ahead of physicians—the ninth consecutive year they ranked in the top three.

Moreover, both the general public and pharmacists want the profession to be more proactive in disseminating information about clinical trials. Market research conducted by the Center for Information and Study on Clinical Research Participation (CISCRP) revealed these two key findings:

- Nearly 80% of respondents would like their pharmacists to tell them about clinical trials, yet only 1% reported receiving this information from their pharmacists.
- In the pharmacist portion of the survey, 56% of respondents said they would be very willing to provide trial information to interested patients/customers.

“The pharmacy channel is ripe for clinical research education, outreach and recruitment, but until now hasn’t been accessed to its full potential,” says Ken Getz, Board Chairman of CISCRP and Senior Research fellow at the Tufts Center for the Study of Drug Development. “The decision to participate in clinical trials is not one a patient typically makes alone. The results of CISCRP’s recent research suggest that people consider community pharmacists a trusted resource, and that these pharmacists serve as an important educational channel that may affect their decision to participate.”

Patient knowledge and insights

In a perfect world, a patient recruitment program would be finely tuned to accomplish both precision targeting (geographic and therapeutic) and sufficient patient volume. The former accelerates the screening process by selecting better-qualified candidates, while the latter ensures the study has enough candidates to meet its enrollment goals. In the real world, however, study sponsors, professional recruitment organizations and investigators often seem to have only two recruitment options: either use a scalpel for precision (i.e., through investigator sites), or a blunt instrument for volume (i.e., direct-to-patient mass-media advertising).

Pharmacy-based recruitment programs can combine precision with reach. Volume is certainly not an issue; there are more than 61,000 pharmacies in the United States, of which 34% (more than 20,000) are independent community pharmacies. These independents on average fill 64,000 prescriptions a year and can be accessed and utilized in aggregate through specialized pharmacy networks. Community pharmacists generally have stronger relationships with patients, which make them well-suited to vet potential candidates.

Pharmacists are also in a unique position to expedite targeting and enable studies to quickly “fill the funnel” with high-quality, pre-qualified potential participants. Geo-targeting obviously can be extremely precise—a major benefit since distance to a clinical trial site is a determinant as to whether patients participate in a trial (a 30-mile radius is the upper limit for most indications except cancer). Therapeutic targeting also can be greatly refined. Pharmacists’ customer databases are brimming with rich, privacy-protected data to target patients with specific diagnoses and co-morbidities, enabling studies to filter candidates based on protocol inclusion/exclusion criteria.

Yet while patient data has always been the allure of pharmacy-based recruitment programs, what really excites industry professionals about this channel is its potential to become truly patient-centric. Pharmacists are the most accessible healthcare providers in the country. Americans visit pharmacies at more than five times the annual rate at which they visit their primary and specialty care physicians combined. Each of these interactions is an opportunity for clinical trial education and, more importantly, gives pharmacists a chance to interact with and learn about their patients. For community pharmacists, these relationships set them apart from the chains and can be instrumental to their long-term success. “What’s sometimes neglected in recruiting strategies is the fact that patients are people,” says Benbrook. “The idea of combining data with pharmacist engagement and patient interaction is an exciting concept.”

For example, the McKesson StudyLink program (see sidebar) is designed to leverage the patient knowledge and insights of 2,500 independent community pharmacies whose patient programs McKesson contractually supports. After doing the first cut of eligibility screening based on geographic proximity (when applicable) and prescription claims data, McKesson sends a list of potential candidates to pharmacists to remove those whom they consider inappropriate. The reasons for exclusion often cannot be inferred using prescription history, and require knowledge that only the pharmacist would have. For example, one candidate may recently have become pregnant; another might be on a medication for a different indication than what the records show; others may have mobility, language, or personality barriers that would make them a poor fit for certain trials.
“My background is in the group practice environment, and this approach is similar to how we find patients by applying filters to medical records,” says Brenda Drake, Director of Business Development, Chase Medical Research, who intends to use StudyLink for an upcoming patient recruitment effort. “It’s helpful to go beyond the raw data, because even medical records aren’t necessarily an accurate reflection of what’s really happening. We know, for example, that patients don’t always take their prescribed medications.”

While it’s important to be realistic about goals and expectations, results suggest that pharmacy-based recruitment strategies could see high rates of success.

Success factors
Since more sophisticated pharmacy-based recruitment programs are relatively new, best practices have not yet been established. Still, the industry’s experiences in partnering with pharmacists on compliance and behavioral intervention programs can provide useful guidance. For example, it’s critically important for any program to avoid disrupting the dispensing workflow. Other success factors are likely to include:

• A contractual relationship with a sufficiently large network of interested pharmacists to meet volume criteria in different geographic areas.
• Legally compliant access to prescription claims and demographic data with the clinical infrastructure and information technology to systematically identify potentially qualified candidates.
• Active involvement from pharmacists in vetting and validating pre-qualified candidates based on personal knowledge of their customers.
• Patient outreach and proactive follow-up to inform and educate patients about the clinical trial opportunity and to confirm eligibility and interest. (Note: This key step was missing in most of the earlier recruitment programs.)
• An operational infrastructure for training and compensating pharmacists while ensuring compliance with federal and state privacy laws and regulations.
• Ongoing communications to participating pharmacists (e.g., updates on the status of which candidates were enrolled in the study) to keep them informed and engaged.

The ultimate determinant of success for such programs will be their ability to deliver demonstrable benefits. For study sponsors, recruiting firms, and investigators, these programs must accelerate enrollment timelines, reduce costs for pre-qualified referrals, and improve referral-to-enrollment ratios. Tracking performance on these and other metrics will provide a baseline for meaningful assessment.

For pharmacists, evaluating the benefits of participating in a clinical trial patient recruitment program boils down to two simple questions: Is this the right thing to do for my patients? Will this be worth my time? Research shows that the public wants more information about clinical trials, with analysis indicating that chain pharmacy users are 26% less likely to be very or somewhat interested than users of locally owned community pharmacies. As to the second question, the answer will depend not just on the compensation pharmacists receive but also on the effectiveness of these programs in promoting and strengthening customer relationships as a key tactic in gaining a competitive edge in their local markets.

Experience with a number of pharmacy-based programs show that many pharmacists find it professionally rewarding to apply their clinical expertise and customer knowledge. Forward-thinking pharmacists such as Tim Davis, the chairman of the National Community Pharmacists Association’s Committee for Innovation and Technology, are embracing new roles and opportunities available through industry partnerships.

“Pharmacies are a critical node in our healthcare system for the collection, distribution, utilization, and management of data,” says Davis, the President of the Revolution Rx consulting firm and the owner of two Pittsburgh area pharmacies, which were both part of a patient recruitment program for a migraine study (see sidebar). “Any programs that will help pharmacists leverage data in new ways, promote better healthcare for patients, and generate revenue streams are extremely valuable to the participants and our profession.”

Kevin Winston, the owner of Sutcliffe Pharmacy in Chicago, cites one more reason for his involvement with clinical trials. “Educating and recruiting patients for clinical trials is personally and professionally rewarding,” he says. “It’s satisfying to know you’re making a difference in your customers’ lives.”

A balm for a chronic pain point
With clinical trials becoming larger and increasingly complex, demand for patients will only intensify. Overcoming enrollment challenges will require innovative, multi-faceted recruitment strategies.

Pharmacy-based patient recruitment programs can be part of the solution. As a complement to more traditional tactics, they can be a balm to help soothe the trial process’ chronic pain point—delays caused by an inability to precisely target and qualify a sufficient number of patients. Pharmacists are motivated to be a conduit for such programs, and patients want to know more about clinical trials. While it’s important to be realistic about goals and expectations, results suggest that pharmacy-based recruitment strategies could see high rates of success.”
References


Steve Hoffman, is Senior Vice President, Chief Pharmacy Officer at McKesson, 4343 N. Scottsdale Road, #370, Scottsdale, AZ, e-mail: steve.hoffman@mckesson.com.

CARDIAC SAFETY IN CLINICAL TRIALS

Adverse cardiovascular events may pose significant costs and change to strategies for preclinical and clinical drug development for both non-cardiac and cardiac drugs. As a result, the need for extensive cardiovascular risk assessment is recognized as an important component of a clinical trial program. This insert will focus on topics that will help Sponsors implement innovative, reliable and regulatory authority suggested methods to identify cardiac safety risks.

SUGGESTED ARTICLE TOPICS*

» Utilizing Translational Research to Accelerate Clinical Trial Phases in Cardiac Safety
» Identify Acceptable Ranges of Blood Pressure and Heart Rate Changes
» Understand and Utilize the Thorough QT Study Effectively
» Case Studies On Innovative Methods of CV Risk Assessment

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Business and People Update

People

• Frontage Laboratories (Exton, PA) announced two senior appointments to lead its clinical services efforts. George Laskaris has been named Senior Director, Frontage Biometrics Services. Alma Villasin, RN, BSN, MBA, joins as Director, Clinical Operations.

• ICON plc. (Dublin, Ireland) has appointed Finance Director Simon Mouncer. Mouncer, who is based at the Milton Keynes headquarters, has been with the company since 2012 in an interim capacity.

• Theorem Clinical Research (King of Prussia, PA) announced the appointment of two top-level executives: Alison Taber as Vice President, Global Data Management, and Jeff Wiley, as Senior Director of Clinical Operations.

• Rho (Chapel Hill, NC) announced the addition of Richard Koenig as Vice President of Operations. In his position, Koenig will lead a growing team of research professionals, including principal investigators, clinical research associates, data managers, biostatisticians, statistical programmers, project, and program managers, and others.

• BioClinica, Inc. (Newtown, PA) announced the appointment of David S. Herron to the position of Executive Vice President, and President of the company’s Imaging Core Lab division. Herron is responsible for the global strategic planning and operations of BioClinica’s medical imaging management solutions, which include software and services for the electronic transfer, management, and independent review of medical images for clinical trials.

• CTI Clinical Trial and Consulting Services (Cincinnati, OH) announced the following new hires: Mark Voge, Senior Regulatory Specialist; Jacqueline Miefert, Senior Study Coordinator; Bonnie Graham, Clinical Safety Scientist; Michael Romes, Research Associate; Thomas Winrod, RN, Associate Director, Clinical Trials, and Paula Ulsh, RN, BSN, Associate Director, Medical and Scientific Affairs. They also announced the following promotions: Sandy Stagge to Director, Clinical Trials; Matt Hodskins to Assistant Director, Project and Proposal Management; Robert McRae to Study Manager, and Erin Kraus to Associate Study Manager.

• ReSearch Pharmaceutical Services, Inc. (Fort Washington, PA) announced that James Pusey, MD, has joined as President and General Manager.

• Chiltern International Limited (London, UK and Wilmington, NC) announced the appointment of Andrew Monaghan, PhD, as Director, Global Pharmacovigilance.

• Drug Safety Alliance, Inc. (Research Triangle Park, NC) a United Drug Company, announced the appointment of Susan Gordon, RN, MSN, to the role of Chief Executive Officer.

• Advanced Clinical (Deerfield, IL) announced the addition of Cheryl Evans, RN, Vice President, Clinical Operations to its leadership team. Evans will be responsible for strategic planning and tactical operations in project management, clinical monitoring, site activation, and document management.

• DIA (Horsham, PA) announced that Barbara Lopez Kunz has been named Global Chief Executive.

• ERT (Philadelphia, PA) announced an expansion of its executive management team.
It has appointed James Corrigan as the company’s Executive Vice President and Chief Operating Officer.

• **Pharmaceutical Product Development (PPD)** (Wilmington, NC) announced it has appointed David Johnson, PhD, as Executive Vice President of Global Laboratory Services.

• **Woodley Equipment Company, Ltd.** (Lancashire, UK) announced the addition of Vijay Manchha as the Business Development Manager for the Clinical Trials Division.

**Acquisitions**

• **Crown Bioscience, Inc.** (Santa Clara, CA and Nottingham, UK), a global drug discovery and development service company, announced that it has acquired the shares of Preclinical Oncology Services Limited (PRECOS), a pre-clinical research and development service provider with a specific focus on oncology.

• **Litera** (McLeansville, NC) announced the acquisition of AxxiTRIALS, a Clinical Trials Portal solution providing life science companies and clinical research organizations with a platform designed to dramatically speed site start-up, patient recruitment, and end-to-end clinical trial operations.

**Alliances**

• **Clinical Site Services International (CSSI)** (Glen Burnie, MD) announced their new partnership with TruBios. The partnership aims to deliver CROs/pharma and biotech clients solutions that are focused on site performance, while also allowing CSSI to expand its site network in Latin America.

• **The Biomedical Research Alliance of New York (BRANY)** (New York, NY) has partnered with ViS Research to streamline feasibility assessment for clinical trials. The collaboration will help medical researchers by reducing their administrative burden related to these feasibility questionnaires while providing faster and easier start-up of the clinical trials.

• **Theorem Clinical Research** (King of Prussia, PA) and Emerge Group have formed a strategic relationship to provide global regulatory consulting services, including reimbursement consultation and in-country regulatory representation services, to the medical device and in vitro diagnostics communities. Theorem has also announced the addition of RadMD, a medical imaging expertise company, to its roster of strategic alliances.

• **HealthCarePoint** (New York, NY and Austin, TX) and ViS Research announced they will connect platforms to improve cost-efficiency in clinical research. The partnership will allow clinical trial planners to quickly access clinical research professionals’ personal experience and training records through the ViS platform, and give clinical research sites access to human resource management systems hosted by HealthCarePoint at no cost.

**Awards**

• **Pharmaceutical Product Development (PPD)** (Wilmington, NC and Conshohocken, PA) and ePharmaSolutions announced that their strategic alliance has been recognized with a Microsoft 2013 Life Sciences Innovation Award, honoring their initiatives in integrating world-leading clinical research expertise and eClinical solutions to advance biopharmaceutical clients’ research programs.

• **Clinical Research Advantage (CRA)** (Tempe, AZ) President and Chief Operating Officer, David M. Bruggeman, was the recipient of two Stevie Awards at the 11th annual American Business Awards. Bruggeman received the Bronze Award for “Executive of the Year” in both the Pharmaceuticals and Health Products and Services categories. CRA’s CEO, Mark S. Hanley, was the recipient of a Gold Stevie Award, recognized as the “Maverick of the Year” in the Business Services category.

• **Almac** (Souderton, PA and Craigavon, UK) Clinical Services team was presented an award by Brent Kelly, Director of Clinical Supply Operations for Otsuka America Pharmaceutical Inc (OAPI). Almac provided clinical supply services for OAPI’s Abilify Maintena clinical trial program, supporting the approval of the once-monthly injectable treatment for schizophrenia earlier in 2013.

• **CFS Clinical** (Audubon, PA) has been named, for the second year in a row, one of the Best Places to Work in the Philadelphia region by Philadelphia Business Journal.

• **Covance Inc.** (Princeton, NJ) has been recognized by Diversity Employers (formerly Black Collegian) for a fourth consecutive year, as a Top 100 Employer in 2013. The Top 100 are selected based on a survey of the hiring plans for major national employers that recruit on college and university campuses for entry-level talent, undergraduate or graduate level.

**Company News**

• **Theorem Clinical Research** (King of Prussia, PA) established a credit facility with GE Capital, Healthcare Financial Services to fund further growth and potential acquisitions. At the end of this year’s second quarter, Theorem reported a 52% increase in total backing since 2011, record revenue and EBITDA, and no long-term debt.

• **IntegReview Institutional Review Board** (Austin, TX) joins the Society for Clinical research Sites (SCRS) as a Global Impact Partner, a designation that includes executive-level participation on the SCRS Global Impact Board.

• **CluePoints** (Cambridge, MA) provider of centralized statistical monitoring (CSM) solutions for clinical trials, announced its CSM techniques have been cited by the FDA in the recent release of the final guidance document detailing the agency’s stance on the “oversight of clinical investigations.”

**New Facilities**

• **INC Research, LLC** (Raleigh, NC) announced the establishment of INC Research Japan KK with the opening of new locations in Osaka and the Shinagawa ward in Tokyo. INC Research now has 28 offices in key locations across the Asia/Pacific region.
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Suicidal Ideation and Behavior: We Can Make a Difference

We in the biopharmaceutical and medical device industry are fortunate to have the opportunity to make a difference in patients’ lives. We develop products that treat a range of conditions, from life-threatening ones to those that help us remain active and vital as we age, with the goal of improving patients’ health. Recently, the FDA has given us the opportunity to make a difference in patients’ lives in yet another way. They are asking us to assess and monitor suicidal ideation and behavior in our patients. Why? And, how can we make a difference?

Meta-analyses conducted by FDA (circa 2004-2009) revealed a signal for treatment-emergent suicidal ideation and behavior in studies of products for depression, epilepsy, weight loss, and psychiatric illnesses. Based upon these findings, FDA issued a draft Guidance in 2010, and then a revised draft in 2012, recommending prospective assessment of suicidal ideation and behavior for certain types of products. Specifically, FDA recommends that “prospective suicidal ideation behavior assessments should be carried out in all clinical trials involving any drug being developed for any psychiatric indication, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system (CNS) activity, both inpatient and outpatient,” (http://1.usa.gov/PmBr9I).

The FDA goes on to recommend that sponsors developing any product that has a CNS effect should assess suicidal ideation and behavior. Finally, FDA recommends that prospective assessment of suicidal ideation and behavior in all drug development programs will allow us to build a wide database that addresses the issues of increased risk, and possible reduction of suicidal ideation and behavior risk for all drug classes.

Many of us may find this guidance daunting. However, if we stop for a moment and consider these recommendations from FDA, they may not seem so overwhelming. We routinely evaluate adverse events in every single trial for every product. If we think about it this way, it’s a matter of working another type of safety assessment into our clinical trial process. This would, thereby, transform this assessment into a routine part of what we do everyday. Yes, this will be work at first.

The practical among us will want to know what effort this assessment will require. The FDA states that there are a number of instruments available for use, including the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS has already been adapted for patient reported outcomes, and incorporated into trials using existing, proven technology, similar to our widespread use of other types of ePRO. Over 100,000 eC-SSRS assessments have been captured to date. When there is not a signal of suicidal ideation or behavior, these assessments take about three minutes for the patient to complete and require little staff effort.

In May of this year, the Centers for Disease Control and Prevention (CDC) reported that there was a significant increase in suicide for people between ages 35 and 64 from 1999 to 2010, and that in 2010 there were 38,364 deaths from suicide in the United States. We touch thousands of lives every day and have the opportunity (one might say the duty) to help reduce this number by prospectively evaluating suicidal ideation and behavior in every trial, intervening if/when we find a signal of risk in any individual patient. We can simultaneously establish a database that identifies signals of risk for specific product classes, and also demonstrate products that might in fact reduce risk of suicidal ideation and behavior. We can and should make a difference.
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