In this BriefingON series, sponsored by ClearTrial, we present a selection of recent stories from Bio·IT World and its sister publication, eCliniqua, that illustrate how new technologies and approaches can have a profound impact on the management and execution of clinical trials.

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For all the hyped new technologies surrounding biomarker discovery and personalized medicine and next-generation sequencing, there is no getting around the fact that clinical trials remain the most arduous and expensive aspect of the drug development pipeline. There is simply no substitute for putting new chemical entities into human volunteers and hoping that all of the computational biomolecular simulation and preclinical toxicity screening that went before has produced a drug as safe and effective as legions of biologists, chemists, and pharmacologists believe it to be.

In this BriefingON series, sponsored by ClearTrial, we present a selection of recent stories from Bio•IT World and its sister publication, eCliniqua, that illustrate how new technologies and approaches can have a profound impact on the management and execution of clinical trials.

Setting the stage are industry expert Ken Getz, who reviews the trends for the staging of clinical trials (“Getz: Industry Trends Suggest More Trials Will Go to Top Sites”) and the results of a recent survey organized by Bio•IT World sister company Insight Pharma Reports (“Efficiency vs. Operation Readiness”).

It is remarkable that in 2010, even one of the country’s most famous cancer centers still doesn’t fully embrace electronic data capture. Nevertheless, the experience of key personnel at the Dana-Farber Cancer Institute provides some valuable insights into the criteria used to select an EDC platform (“Integrating InForm EDC at Dana-Farber Cancer Institute”). On the other hand, the remarkable growth of social media is providing a welcome boon to patient recruitment strategies (“A Social Approach to Patient Recruitment”), while a French company, spun out of the Institut Pasteur, is making headway by applying data mining tools to clinical trials (“Ariana: Bettering Trial Design with In-Depth, Multi-Endpoint Analysis”).

The value of electronic health records (EHRs) in facilitating the participation of physicians in clinical trials is well made in an expert commentary (“Clinical Trials and EHRs: Incentive to Integrate”) while software from ClearTrial aids significantly in project and financial tracking of clinical trials (“ClearTrial Adds Project Tracking Product to Integrated Software Suite”).

Finally, lest we forget, pharma companies – in this case Lilly – are not averse to shaking up their organizations in a high-stakes effort to boost productivity throughout the pipeline (“Lilly: New Operating Model will Speed Tailored Therapies to Market”).

We hope you find some useful material in this BriefingON.

Kevin Davies, Deb Borfitz and Allison Proffitt

Bio•IT World
Sponsors need to think about patients as partners that help them complete trials,” says David Williams, chief marketing officer of six-year-old patient advocacy site PatientsLikeMe. “It’s a sacrifice in a lot of ways, not part of their normal routine.” PatientsLikeMe fell into the recruitment business when study sponsors recognized it as a viable source of motivated trial participants. When joining one of the site’s 19 condition-specific online communities, members understand that anonymized data about their symptoms, treatment, and outcome will be shared with select pharma companies in search of real-world insights—and possible trial participants. The click-through rate to the online pre screener is 42%, almost triple the industry average for email marketing campaigns.

Although average recruitment speed has improved over the past decade, from roughly 24 months to nine months currently, target recruitment timelines have tightened such that most clinical studies continue to take at least one month longer than planned to hit enrollment goals, says Bonnie Brescia, co-founder and president of BBK Worldwide. And Jeanine Estrada, director of business development at CRO Clinilabs, points out that most if not all forms of traditional advertising are decreasing in effectiveness. Insufficient numbers of enrollees is the top reason trials get delayed or abandoned, but the problem may be largely correctable by tapping into the legions of health-conscious people in social online settings, says Leigh Fazzina, principal with Fazzina & Co. Communications Consulting. To be warmly received, sponsors need only engage patients in conversation and play by the rules of their gathering places.

Winning Approaches
Since recruitment accounts for only about 4% of its revenues, PatientsLikeMe has no incentive to “over-promise,” says Williams. The company also avoids hyperbole and even the term study “subject,” widely embraced in recruitment circles, believing it engenders distrust. “A patient is a person, not a mouse,” says Williams. PatientsLikeMe has a strict protocol vetting process to ensure that trials promoted to community members are scientifically sound and clinically significant. Novartis says that PatientsLikeMe helped accelerate its trial of an oral medication for people with multiple sclerosis (MS). “We were more than happy to do that one because it was a breakthrough delivery system,” says Williams. “Treatments on the market today are only delivered by injection.” Less than 10% of initial trial promotion requests are honored, half the time due to the protocol. Other sponsors balk at the service fee, based on a combination of community size, disease prevalence, and ease of identifying qualifying patients.

Several social networking sites have the potential to bridge the gap between those offering and seeking a clinical trial, including social support network WeAreUs, NexCura (oncology), and 23andMe (genetic testing). SharingStrength.ca, a Canadian online resource and community for women with breast cancer, encourages researchers to post trial enrollment opportunities to patients. Clinical trial listing sites ClinicalConnection and Medpedia promote trials on Twitter, effectively driving people to their sites for screening. Among the most promising outreach tools are Inspire, which introduces trial opportunities to disease-specific communities, and Acurian, which distributes email solicitations to appropriate individuals in its opt-in database while raising trial awareness through an application on Facebook and MySpace.

Academic medical centers like UCSF, Vanderbilt, and the Mayo Clinic do a good job on a regional basis with a trial matching service. MD Anderson Cancer Center has cast a wider net by creating a web link from Facebook to whisk interested “friends” to information about its clinical trial offerings, says Carmen Gonzalez, communications manager at the Health Care Communications Group. Mayo also offers tutorials to help other health care providers “wet their feet in social media.”

Singapore- and Silicon Valley-based startup Bubble Motion is making a splash with Bubbly, a voice version of Twitter, in India and Brazil where telephony and mobile phone infrastructure outpaces web access. In the U.S., the non-profit Center for Information and Study on Clinical Research Participation (CISCRP) launched an iPhone application that stores trial-related educational and reference material, provides a link to an online newsletter, and connects users to CISCRP for cus-
comitant conditions, where intelligent
recruitment management system (TCN e-
systems) that also helps project managers
pick the right sites and countries and sites approach patients about trial oppor-
tunities.

There are other players in the trial planning and design category, including
DecisionView (Study Optimizer), Provisio
(iTrials), Trialytics, and i3 (i3Cube), all of
which have built databases aggregating
information from clinical and non-clinical
sources. Their relevance to a study may
depend on the geographies and patient
types represented in the underlying data-
bases.

The database solutions work largely by
manipulating existing data to answer
sponsor queries, but the information
tends to be “relatively static” and therefore
of limited value, says Estrada. “People are
interested in participating in a clinical
trial at one point in time” and by the time
they’re identified in a database, their
health status and life circumstances may
have changed. Thus database products
may require updating monthly to be truly
effective.

That’s not a problem for Provisio’s iTri-
als database (DirectConnect), remotely
accessible, in real time, to sponsors and
cROs via cloud computing, says David
Bender, head of sales and marketing at
Provisio. It was built from scratch out of
80 million individual patient health histo-
ries and represents 500,000 health care
providers and 100,000 treatment facili-
ties in the U.S. For purposes of assessing
protocol feasibility or predicting and re-
cruiting more effective study sites, that
gives study planners more than 15 billion
relevant data points to run inclusion and
exclusion criteria against. Physician data
is organized to assess potential trial par-
ticipation as an investigator or the likeli-
hood of referring patients to trials.

DirectConnect improves recruitment
rates by at least 33% because patients are
fully pre-qualified for a trial prior to being
contacted about the opportunity.

DirectConnect is especially suited to
more complicated studies, such as those
involving a drug washout period or con-
comitant conditions, where intelligent
decision making requires a high confi-
dence level with speedy access to longitudi-
nal health information, says Bender.
Provisio recently helped a company con-
ducting a juvenile growth hormone study
identify patients who had just been diag-
nosed with a growth deficiency and not
yet on a conventional therapeutic. Informa-
tion in a re-purposed database would
have been too dated to answer the query.
BioMimetic Therapeutics reports that
iTrials solutions saved it $1 million over 12
months by directing it to sites with pre-
qualified patients.

All the major pharma companies have
begun investigating the feasibility of using
electronic health records (EHRs) to iden-
tify potential trial participants, says Wil-
liams. But outside of the data-sharing
world of PatientsLikeMe, implementation
could be tricky. People won’t necessarily
respond favorably to a trial opportunity
knowing they were identified by a scur-
ing of their private medical records. An-
other complication is that EHRs were
created to “improve care, reduce redund-
ant procedures, and avoid medical inter-
actions,” not to be queried in support of
clinical research, adds Brescia.

A more immediate possibility is a smart
phone that transmits personal
health and activity data to digital health
records via wearable sensors, an idea be-
ing researched at the West Wireless
Healthy Institute in San Diego. The idea is
to quickly catch and treat emerging medi-
cal problems, says Gonzalez, but it will
also create electronic profiles of patients.

In the aggregate, these patient profiles
will allow clinicians to improve the treat-
ment model for all patients. Gonzalez en-
visioned the same information being used
to identify patients who might qualify for
a given trial.

Building Relationships
No one technology will cure all that ails
trial recruitment and the best combina-
tions of tools are disease- and audience-
specific, says Brescia. “We’ve enrolled
an entire study in less than one month using
[strictly] an online strategy and in other
cases to supplement the traditional [off-
line media] approach, bringing in no
more than 10% of total patients.” Online
outreach provides “tremendous rele-
vance,” making it greatly more cost effec-
tive, but often can’t provide the reach of
television.

Chris Trizna, president and owner of
Clinical Site Services, hopes to address the
potentially huge number of enrollees at
stake and ease sites’ call burden with an
automated phone screener system de-
dsigned to weed out 30-40% of callers who
don’t meet minimum study criteria or
don’t want to travel to the trial site.

Investigative sites could be encouraged
to build their own database and targeted
e-mail campaigns, says Estrada. They
could potentially create online communities
specific to their practice or trial par-
ticipants, with linkages to the major social
networking sites based on search terms
like “clinical trial” and invitations to be a
friend or follower of the group. Unfortu-
nately, commercial institutional review
boards (IRBs) have yet to develop specific
guidance for investigators inclined to
blaze the social media trail.

The strategy can nonetheless be effec-
tive over the long term, and not simply to
rescue a single, recruitment-challenged
study, says Estrada. “A community doesn’t
get built overnight. It can take time for
social networks to establish themselves,
and someone needs to encourage them to
grow.” The advantage of growing a social
network at the site level is that it comes
with a level of familiarity that breeds trust
and spreads it virally. In the first months
after Clinilabs established a Twitter ac-
count, 76 people became followers of a
website developed for its clinical research
unit, which provides regular updates
about the two dozen or so trials it con-
ducts each year.

Health Care Communications Group
tutors sites about how to harness social
media before promoting trials. Using
third-party geo-location tools like Nearby
Tweets, they can immediately respond
with an IRB-approved recruitment mes-
gages when a Twitter user within a pre-
scribed perimeter uses disease-related
keywords like “back pain” or “Alzheimer’s
disease.” Once sites start to see a “return
on connections,” Gonzalez expects their
efforts will be further supported by trial
sponsors. Sponsors seeking to align their
recruitment aims with patient needs are
advised to support the online initiatives
of patient advocacy groups, at “arms length”
for transparency.

One sponsor client had surprisingly
good results using social media, even
though it insisted on shielding its identify
and that of the study drug. “For every 80
messages, we received 20 visitors to the study web site,” she says. “People were very warm ... [and] thanked us. Imagine what we could have accomplished if we had a rapport [with our followers] and were perceived as actively engaged.”

Recruiting for trials on Facebook has proven successful in certain diseases. Clinical Site Services found the site out-performed Google and Yahoo placement ads “five to one” for a sexual desire study targeting young females, says Trizna. For an HIV study, Facebook also produced at least twice as many clicks.

Pop-up advertisements can be triggered on Facebook based on keywords in an online profile, such as diabetes, or being a fan of groups like the National Multiple Sclerosis Society, says Williams. His advice to sponsors is to stop lauding the benefits of participating in research, because the advantages are neither immediate nor guaranteed, and stop assuming patients with a chronic illness feel lucky to be in a clinical trial. “They might be more willing to participate based on the severity of their condition, or because they have a rare disease, but those are few and far between. Perhaps most importantly, sponsors need to start engaging in online conversations to de-mystify the clinical trial process, aid informed decision making, and give hope. That’s what motivates patients to participate.”

Guiding Lights

The adoption of social networking sites as communication channels now out ranks natural search engine optimization, but life science companies have been understandably cautious given their legal and regulatory constraints, says Fazzina. The last time the U.S. Food and Drug Administration (FDA) issued guidance about online interactions with consumers was in 1996—a year before the launch of Amazon. The FDA began a one-year, fact-finding mission last November intended to conclude with industry guidance related to the online marketing and social media communications of pharma and medical procedures and, it is hoped, information exchange about clinical trials and patient recruitment.

A letter submitted to the FDA by Fazzina, Gonzalez, and others entreaties the agency to craft “adaptive” social media communications guidelines following existing models governing live media interviews and media tours via television and radio. The advocated policy would maintain IRB sovereignty over content while providing latitude to answer unanticipated questions, use acronyms and abbreviated messages, and do non-study-related messaging in keeping with social networking etiquette. “Simply sending IRB-approved promotional messages about a clinical trial without using the medium in ways typical of a common user raises suspicions of spamming,” they point out. Separately, a few companies suggested FDA give its “stamp of approval” to all legitimate online postings.

Sponsors have to date used social networking venues cautiously and almost exclusively as a one-way communication vehicle, either to eavesdrop on patient conversations or to deliver information about health conditions. However, two-way communication is an even more potent means to raise trial awareness, particularly if sponsors understand that they can wield control by creating their own sites and limiting membership to people with a certain medical condition. The longer term task would be to build relationships with a growing base of followers, creating a pool of potential subjects for studies in a particular therapeutic area. BBK has online communities for diabetes, asthma, and MS for about 20% of the sponsors enlisting its recruitment expertise.

A simple hashtag in front of keywords like “clinical research” or “clinical trial” can effectively serve as a study search engine on Twitter, adds Fazzina. Social networking venues don’t come with an instruction booklet but nonetheless have their own language and rules. Any message sent out by a corporation needs to be consistently “spot on” and thus formulated by a single governing group—an apparent shortcoming of several CROs with multiple Twitter and Facebook accounts.

Dialogue about clinical research within social networking sites and blogs can be easily monitored and measured by social media monitoring services, much like a traditional news clipping service, to understand public sentiments and respond accordingly. “There is currently a lot of online discussion in social spaces about back pain and migraine headaches,” says Fazzina. Patients are looking for information and want options, she says, but she doesn’t see pharma getting involved and taking advantage.

While trial sponsors are under-utilizing the tool, some recruitment vendors are blatantly disregarding rules set forth by the Health Insurance Portability and Accountability Act by soliciting private health care information on social networking sites, says Gonzalez. These are “red flags” of overdue FDA guidance.

It may be years before FDA clarifies its position about trial recruitment via popular social networking sites. Existing subject protection principles and marketing guidelines for FDA-approved drugs are usually sufficient for the online environment. “The internal requirements and guidelines of sponsors, set up for risk mitigation reasons, are generally more restrictive than those of external regulatory groups,” says Brescia. Ironically, the companies moving most aggressively into the social networking arena have no corporate-wide rules for engaging people online. In their view, the potential gains in terms of product marketing and trial recruitment outweigh the peril of mixed messaging.
Expert Commentary

Clinical Trials and EHRs: Incentive to Integrate

(Originally published March 2010)

Clinical trials should play a much bigger role in the decision to purchase electronic health records (EHR) software. One incentive for practices is that participation in clinical trials has the potential to net a profit of hundreds of thousands of dollars per year. Using EHR data in clinical trials is a win for physicians, patients, the companies conducting clinical trials and the entire health care system.

While there are many factors that go into an EHR software purchase, clinical trial participation deserves more consideration because:

- Participating in these trials is easier through an EHR than through traditional paper means;
- Using EHR data solves many of the major problems that clinical trials face; and
- Purchasing an EHR creates a big ROI for physicians who decide to participate in clinical trials.

**EHR Software Facilitates Clinical Trial Participation**

According to Synergyst Research, only 10% of licensed physicians participate in clinical trials. Major reasons include the extra burden that research and information collection place on a practice's time, staff and resources. Extra paperwork and onerous regulations are involved, not to mention training staff on how to properly complete forms and follow protocol. The average practice would find it difficult to find the resources to create a new department devoted to clinical trial participation.

Those using EHRs, however, stand a better chance of being able to adapt to the needs of a study. There are several that EHR software can make the clinical trial process faster, more efficient and more accurate:

- **Identify potential opportunities:** EHR vendors whose software integrates with clinical trial providers will have access to trials, studies, and registries that your practice is eligible to participate in.
- **Identify number of potential trial subjects:** The search function in an EHR database allows users to quickly identify how many patients are potentially eligible for a clinical trial. From there, the clinical trial provider can determine if a practice would be a good partner.
- **Patient enrollment:** The EHR has the capability to implement trial-specific screening requirements into new patient records to determine their eligibility for a study. The EHR will also have the ability to identify patients who meet the exact requirements of a study.
- **Study execution:** During the trial, the EHR can create trial-specific data fields that can be populated during routine patient encounters. Conflict alerts can also be created to notify providers of actions that violate a study's protocol.
- **Data submission:** The EHR will be able to submit information to EDC software without having to convert the data. This eliminates redundant data entry and increases accuracy of the data.

By using an EHR to do much of the patient identification and information collection, many of the previously mentioned obstacles no longer exist. If a practice purchases EHR software that doubles as an electronic data capture (EDC) system for clinical trials, then it is way ahead of the curve in terms of efficiency and accuracy.

**Clinical Trials Are Important to the Future of Health Care**

We all know the alarming cost and time required to bring a new drug to market, not to mention the 75% failure rate. This mediocre productivity leads to increased health care costs and patient suffering as drug approval is delayed. If clinical trials could be completed more quickly using EHR software, it wouldn't just be drug companies that benefit. Sick patients waiting on essential treatment would be treated more quickly, health care costs would be reduced, and the conclusions reached from the data gathered would be more robust.

**Get a Stronger Return on Your EHR Investment**

The chief areas of return on investment (ROI) on EHR purchase include: reducing the need for transcription services; improving insurance claim coding; reducing paper supply costs; and improving chart management. These are all good, but we believe the profit from participating in clinical trials is just as great a benefit. For example, soon after the Holston Medical Group (HMG) in Kingsport, TN, began using an EHR in 1996, the company began participating in clinical trials using the data from their EHR. HMG's EHR influenced their involvement in clinical trials in three major ways.

First, HMG is able to quickly query their EHR database to see which patients qualify for particular studies. Next, the
scope of patient information contained within their EHRs helps improve accuracy when screening patients for clinical trials. Finally, HMG’s EHR is web-based, which means that its doctors always have access to the latest patient information, no matter where the doctor is located.

As clinical trials become more protracted and expensive every year, it’s inevitable that drug companies will turn to those organizations that can quickly and accurately assess patient data. More than likely, those organizations will be using EHR software.

Chris Thorman blogs about medical technology at Software Advice, a website that reviews software for EHRs. See: http://www.softwareadvice.com/medical/electronic-medical-record-software-comparison/. This commentary is adapted from Chris’ blog: Electronic Health Records and Clinical Trials: An Incentive to Integrate.
Efficiency vs. Operation Readiness

(Originally published March 2010)

For most biopharmaceutical companies, the pressure to improve clinical trial portfolio management efficiency has arrived sooner than their operational readiness to meet the challenge. Corporate intolerance for budget variances above 5% of target is now commonplace. But widespread absence of project-level operational metrics has made it all but impossible to drive planned-to-actual spending into alignment.

So suggests the findings of a recent research study, Trends in Portfolio Management, commissioned by Chicago-based clinical trials operations software provider ClearTrial. Results were based on a survey of 94 biopharmaceutical companies by Insight Pharma Reports.

Just two years ago, only 7% of survey respondents had to manage to a 5% acceptance variance on their portfolio budget, reports ClearTrial CEO Mike Soenen. That figure has climbed “dramatically” to 33%, with 67% of respondents having to stay within 10% of target. “You can’t fix what you can’t see,” he observes. In the absence of project-level information, companies can neither competently manage study portfolios nor reduce the margin of error in their long-range planning. “They lack the visibility to achieve their goals.”

The survey found that 64% of respondents lack confidence in their one-year horizon of project timelines, although meeting timelines rates as the number one measurement of portfolio management performance, notes Soenen. Similarly, 60% of respondents lack confidence in their one-year portfolio budget, the number two performance measuring stick. Confidence in one-year portfolio personnel capacity forecasts, critical to having “the right personnel available at the right times during the course of a study,” was lacking among 57% of respondents.

Improving performance measurement and goals is the top way surveyed companies are attempting to cope with the “operational gap,” followed by improving software and systems. Among large biopharmaceutical companies, re-organization was the third most frequently listed initiative. Soenen views the fact that companies are starting to centralize clinical planning as validation of ClearTrial’s integrated “plan to payment” approach to streamlining clinical operations, which should further strengthen its market position.

Enabled Efficiency

The experience of Abbott Vascular suggests ClearTrial software can be a key enabler of otherwise elusive efficiency gains. Last year, the software helped the device maker keep clinical trial spending within a mere 1% of target, reports Thomas Engels, director of clinical program management. In prior years, costs were running 12%-15% under budget because of unanticipated delays in trials start-ups and overly optimistic planning. The software provides visibility across the study portfolio, allowing spending on some trials to offset under-spending on others. Underlying country-specific metrics about timelines, costs, and currency exchange rates also streamlined the company’s first-ever negotiations with Chinese service providers.

Astellas Pharma Global Development has publicly reported that in comparative tests of completed trials to what the ClearTrial system would have predicted as the total budgets, the ClearTrial estimate consistently came within 5% of actual costs. Typically, ClearTrial software saves large and mid-size customers 10%-17% on overall clinical trial costs, says Soenen.

ClearTrial helps companies operate “tighter to plan” by giving them activity-level visibility for performance planning and tracking as well as a central, searchable, and accessible repository for all institutional knowledge. Embedded market intelligence allows for rapid scenario planning and more accurate up front budgeting.

The current “norm” is for time-pressed upper management to declare study milestone dates and budgets without regard for how studies get done and then leave stressed project teams to independently figure out how to hit those targets, says Soenen. Fully 76% of survey respondents say they’re under growing pressure to improve portfolio management efficiency and 80% expect that pressure to increase further next year.

Insight Pharma Reports is now conducting in-depth interviews with a subset of respondents to probe the underlying initiatives and processes of companies able to stay within 5%-10% variance between planned and actual portfolio budgets, says Soenen. That research will conclude with the publication of portfolio best management practices on the ClearTrial website in March 2010.
Getz: Industry Trends Suggest More Trials Will Go to Top Sites

(Originally published December 2009)

Financial conditions for investigative sites look “pretty bleak,” but top-notch sites are well positioned to benefit from growth in clinical trial volume as the economy recovers, according to industry trends data presented by Kenneth Getz, senior research fellow at the Tufts Center for the Study of Drug Development, at October’s Site Solutions Summit in Clearwater Beach, FL. At the moment, dedicated sites are being pinched by price competition from novice sites while academic institutions continue to give up market share to the private sector. Sites overall might do well to acquire the performance jitters, as currently less than 10% of them are delivering on promises made during feasibility assessments. Maintaining the status quo is not an option for trial-sponsor companies struggling to move promising compounds to market before their blockbuster products fall off the patent cliff.

Grant spending is now a nearly $9 billion market growing at a 7%-8% annual clip, “the majority of it coming from industry,” says Getz. The typical investigator today is a white MD over the age of 50 with an urban or suburban-based private practice. Surprisingly, only about 25% of the $7.3 billion in industry-funded projects were placed at sites dedicated to clinical research last year and only 28% of those were managed networks as opposed to single sites. Academia, which accounted for a 70% share in 1994, consumed only 36% of the total. Some academic institutions, including Mayo Clinic, have exited industry-funded clinical research completely.

As of 2007, 57% of all clinical research regulated by the U.S. Food and Drug Administration (FDA) was conducted domestically, says Getz. A decline in the number of U.S. investigators is being offset by increases across Central and Eastern Europe, China, India, and Latin America.

Historically, global drug development spending by sponsor companies has been growing about 11% annually by sponsor companies without a commensurate rise in productivity, says Getz. “It still takes seven years from IND [Investigational New Drug application] to market launch and regulatory review and approval times have gone up, even with PDUFA [Pharmaceutical User Fee Act].” Moreover, most drug approvals now include a mandate for companies to do post-marketing studies.

The Revenue Squeeze

Industry turned out 20 novel molecular entities this year, up from 17 in 2007 but down a bit from 24 in 2008, says Getz. Sixty-one percent of promising compounds in the R&D pipeline are in the discovery/pre-clinical phase and only 16% of drugs that make it into human testing end up on the commercial market. “If the success rate improved even slightly, it would have huge implications on commercial pipeline performance.”

Companies are putting increasing focus on both the pre-clinical and first-in-man development phases to get a better, earlier read on the promise of new drug candidates, says Getz. “First-in-class drugs now have only one year of exclusivity before other drugs [start to] chip away at market share.” Companies make back their investment on only 20% of approved drugs. One-fifth of the commercial portfolio of major pharmaceutical companies is at risk of generic competition within the next five years. That represents a huge amount of revenue loss, he notes, as a product loses 80% of its market share within 18 months of patent expiration. Since companies can’t rely on blockbuster drugs to recoup expected revenue loss, they are instead quickly conducting follow-up studies for new indications.

Clinical research organizations (CROs) provide half the total capacity needed industry-wide amidst considerable downsizing and merger-and-acquisition activity, says Getz. Since the third quarter of 2008, sponsors have terminated or left unfilled over 50,000 positions—7,000 directly for R&D—and are “looking for partners to pick up that slack.” Sponsors and CROs alike are now willing to spend more to stimulate better site performance.

Focus on Performance

From sponsors’ perspective, the “real top performers” (responsible for 50% or more of enrollees) constitute only 20% of all sites year after year, says Getz. Among active INDs, 14% have at least one complaint about an investigator filed with the FDA. Turnover is problematic among...
Bio•IT World Briefing On: eClinical Trial Technologies

both study monitors and study coordinators. “Ninety percent of all trials are delayed an average of six weeks,” no small matter given the $30,000-45,000 per site price tag to keep a study open a single day.

Compliance-related activities are costing companies half of their entire clinical trial budgets, says Getz. This includes Good Clinical Practice review at each investigator meeting, “which can be an insult to [experienced] study staff.” The added sting is that the number of patients per active New Drug Application is “sharply declining” at the same time the average number of investigators is rising, “making it harder for sites to be profitable.”

Sponsors have been trying to use demographic and psychographic data to predict site performance, continues Getz, when the only reportedly reliable statistic is sites’ ability to enroll their first patient within 90 days of study start. During later phases of clinical development, companies tend to use metrics from electronic data capture and clinical trial management systems to “pit sites against each other.” They also will “engage additional sites but not start them until another site fails.” One of the more positive developments is that sponsors are willing to secure “more integrated, coordinated relationships” with preferred sites, including seeking their input on protocol design. A chief challenge is that few sites are willing to accept and few sponsors want to guarantee a certain level of clinical trial work.

Shift in Study Placement
Collectively, these industry trends will drive a shakeout among “marginal” part-time and dedicated sites across the U.S. and Western Europe and be a catalyst for “more retrenchment among institutions that rely on [federal] stimulus money and NIH [National Institutes of Health] grants,” says Getz. The slowdown will extend into emerging regions, with more studies being placed in India or China in lieu of Central and Eastern Europe.

Long term, the more committed sites should be rewarded with a higher volume of research, says Getz. “We’ll see regional shifting as drug development becomes more personalized and sponsors seek a more [genetically homogenous] population. The pressure will be to...place more studies back in the U.S.” For phase I studies, sponsors are already preferentially placing studies back in North America and Western Europe, he adds.

Problematic Protocols
“Within five years, I think we’ll see a totally different relationship between sponsors, CROs, and sites,” says Getz. “Not enough attention has been paid to the fundamental problem of public trust [of clinical research] and protocol design.” Failure to adhere to the protocol is the most common non-compliance issue. Equally troubling is the huge number of seemingly unnecessary procedures that study subjects endure, which has been growing 7% annually. “Up to 30% of data collected [by industry sponsors] is never used for an FDA submission.” Coupled with an eligibility criteria list that has ballooned to include more than 45 inclusion and exclusion items, the excess procedures have helped increase the “execution burden” on sites by 11% per year. Yet compensation per procedure is down 8%.

“More complex protocols have harmed the performance of sites,” says Getz, pointing to growth in the number of case report form pages from 55 to 180 between 1999 and 2006. Cycle times are “substantially” longer and enrollment rates are worsening, with the screen to randomization rate falling from 75% to 59%. The randomization to study completion rate is likewise dropping, from 69% to 48%.
ClearTrial Adds Project Tracking Product to Integrated Software Suite

(Originally published November 2009)

With the latest update to its web-based clinical trial software, ClearTrial has integrated study planning with project and financial tracking to help life science companies better visualize where they can reduce costs and add velocity to the trial process without sacrificing accuracy and quality of results. ClearTrial Track, the latest addition to the software suite, makes ClearTrial v3.0 the only system in the industry enabling fast and accurate project tracking, management of accrued liabilities, and re-forecasting for change orders and midstream study adjustments, says CEO Mike Soenen.

For the folks in clinical R&D finance, in particular, this is the Holy Grail of resource planning and study management. “Everyone tracks like crazy in this industry, but still don’t know where they’re supposed to be...or where they’re headed,” says Soenen. Clinical trial management systems, focusing as they do on clinical activities rather than clinical operations and forecasting, can offer limited guidance. ClearTrial accomplishes those tracking and forecasting tasks quickly and easily, requiring no accounting know-how on the part of users.

ClearTrial Track is part of the company’s ongoing response to the “overarching need to be more efficient and cost sensitive in the whole R&D process,” says Soenen. The integration of clinical operations and financial functions from “Plan to Cash”—ClearTrial’s marketing mantra—achieves speed and savings by identifying and eradicating only non-value-added process components.

ClearTrial Plan is the “prerequisite” to utilizing ClearTrial Track, since a realistic view of study progress depends on the objectives going in, says Soenen. The integrated product essentially allows decision makers to make informed choices regarding how to keep studies on track based on original budgets and timelines.

When dealing with clinical people, a fast and easy-to-use system like ClearTrial is the “cost of admission,” says Soenen. “We extended that with ClearTrial Track by incorporating a complex but proven project management technique, known as earned value management, tailored for use in clinical development.” Project health gets calculated automatically based on ClearTrial Track’s accruals management capability that derives costs from study-related tasks that need to be completed, as detailed in the initial project plan. It’s the same methodology clinical research organizations use to estimate their costs, albeit with an Excel spreadsheet.

Gloomy mid-study forecasts about project end dates and budget overruns can become the catalyst for change orders and protocol amendments that ClearTrial Track also accommodates, says Soenen. The product can easily reforecast and re-baseline studies that are underway while maintaining an audit trail of changes to assumptions and their downstream impact. The budget, resource/FTE, timeline, and unit price impact for the remainder of the study also gets automatically calculated.

“Trial sponsors typically have to engage their financial people to do their reforecasting,” notes Soenen. “Now, clinical people can do it. The software speaks to end users in their language and links clinical assumptions [such as added study visits or an extended subject enrollment period] to the projected financial and timeline impact.”

In addition to ClearTrial Plan and ClearTrial Track, ClearTrial’s “Plan to Cash” software suite includes ClearTrial Source to help accelerate the outsourcing function. Collectively, the three products provide the industry’s most comprehensive integrated management platform for clinical trials, says Soenen.

ClearTrial v3.0 includes expanded currency support and the setting of exchange rates, accommodating the shift to global clinical development, says Soenen.
Ariana: Bettering Trial Design with In-Depth, Multi-Endpoint Analysis

(Originally published April 2010)

Paris-based Ariana Pharma has a decision support platform, known as KEM (Knowledge Extraction and Management) Clinicals, which can be used to complement statistical analysis software like SAS to mine otherwise neglected clinical trial data and optimize the design of subsequent protocols. With the technology, the company can “guarantee [sponsors] we have exhaustively looked at every combination of patient characteristics” to hypothesize which subject types will benefit most from the experimental treatment—and then test those theories against multiple endpoints, says CEO Afshar. Traditional statistical methodologies are better suited to larger numbers of patients and focus on one objective at a time—say, pain relief or improved functional response. KEM Clinicals thus helps trial sponsors focus a product’s indications and explore endpoints earlier in the drug development cycle.

Coupling of the two technologies allow hypothesis testing on phase II and both large and small phase III trial data, says Afshar. KEM Clinicals is stand-alone software with a graphical interface, says Afshar. It was developed in collaboration with a French public research group and four biopharmaceutical firms—GlaxoSmithKline, Pfizer, Novartis, and Merck & Co.—and has been in use for over two years now.

Data mining tools of this type are used extensively to dissect consumer behavior and to detect safety issues in other industries, says Afshar. “In clinical trials, they’re very new. That’s why we’re getting so much interest now.” Currently, Ariana is working with about 20 large pharmaceutical companies. Interest is building among small biotechnology firms “even keener to protect their investment and maximize the amount of information they can extract [from studies].” One of its latest clinical design optimization projects is with Fovea Pharmaceuticals, based on analysis of data from phase II trials of its ocular drug Pednisporin.

Ariana, founded in 2003, is a spin off of the Institut Pasteur. It now does business in the U.K., U.S., and Switzerland in addition to France.

Sponsors have used KEM Clinicals to fashion successful trials based on lessons from failed trials, says Afshar. They’ve also used the technology to produce additional information about a drug’s therapeutic benefit for specific sub-populations, with a positive impact on product pricing. When faced with the dilemma about which endpoints to use, companies have employed KEM Clinicals to rank the alternatives in order of achievability.

In the realm of personalized medicine, KEM Clinicals could be used to look at combinations of patients’ phenotypic features along with their age, gender, weight, disease stage, and treatment history to even more precisely predict treatment outcomes, says Afshar. “There is currently a huge body of data captured in clinical trials that is never used unless something goes wrong.” Ariana is already using its technology to analyze combinations of genomic and biological biomarkers that can be used diagnostically to stratifying patients within established disease categories.
As of this year, Eli Lilly and Company is converting to a new operating model designed to streamline drug development and better “capture the value” of a record-setting number of new medicines in its pipeline. The enablers include a flexible project management approach, routine use of advanced analytics and adaptive trial designs, and a focus on tailored therapies, says Tom Verhoeven, PhD, senior vice president and co-leader of the Development Center of Excellence.

The fresh approach has integrated all clinical specialties and capabilities necessary to bring innovative medicines to market, says Verhoeven, including the newest functions associated with analytics and medicinal tailoring. “We’re not just changing the organizational chart; we’re building a system that allows [functional] groups to coordinate activities with each other on a single process map across study phases and even post-approval.”

The ultimate goal is improved medical outcomes for individual patients with therapies that also create value for payers and providers, says Verhoeven. Starting in 2013, Lilly hopes to be producing two new medicines annually.

The more immediate benefit is eliminating bottlenecks in clinical planning, most notably the “downtime” between clinical trial phases that can slow study start-ups by weeks or months, says Verhoeven. Lilly relies on the “critical chain” project management technique, unfamiliar to most of the pharmaceutical industry, that reflects the way functional specialties are interlinked and responds immediately to incoming data. He compares the approach to a relay race where the focus is as much about the baton pass as a runner’s particular leg of the relay. The idea is to proactively identify and rectify potential “pinch points” in a project.

The pharmaceutical industry has traditionally moved milestone to milestone as if on a train schedule which, while somewhat predictable, is largely immutable and “rather antithetical to innovation.”

Lilly put 5% of its clinical projects into pilot testing with the critical chain methodology over the last few years, with “stupendous” results, says Verhoeven. “On all of those projects, 100% of major milestones were met on time or early.” Historically, Lilly hit those targets only 40% of the time. The company now utilizes the critical chain approach across its portfolio of roughly 60 potential medicines and has yet to miss a delivery mark. This has demanded that Lilly’s relationships with clinical research organizations (CROs) and other external providers be more partnered than transactional in terms of study planning and execution, he adds. A hodgepodge of homegrown information technology solutions across functional groups has also been integrated into a single operating system to “increase communication and interdependence.”

Advanced analytics and greater reliance on cloud computing are critical to Lilly’s operational model. Simulation and modeling, using pseudo-data about study outcomes anticipated by disease-state experts, help ensure the company designs trials likely to produce the most relevant information, says Verhoeven. Adaptive trial designs and Bayesian statistical techniques are also embraced, allowing data that accumulates during a trial to redirect its course. A more sophisticated approach to data mining provides visibility to trends and the wherewithal to make inferences.

The search for tailored solutions is now the foundation of drug development at Lilly, says Verhoeven, leading the company to embrace rather than try to expunge heterogeneity in trials. A “tailoring hypothesis” about a compound’s potential benefit to a certain sub-group of patients is tested during all phase I trials.

Lilly has capitalized on those opportunities. For example, clinical trial data has led to regulatory approvals for and the tailored use of Alimta in the treatment of patients with advanced non-small cell lung cancer with a nonsquamous histology. As part of its new operating model and $1 billion reduction in operating expenses, Lilly will reduce its employee head count from 40,000 to 35,000 by the end of 2011, says Verhoeven. Moving forward, Lilly is interested in longer term relationships and establishing preferred partnerships with CROs and investigative sites, he adds.
Integrating InForm EDC at Dana-Farber Cancer Institute

(Originally published May 2010)

The Dana-Farber/Harvard Cancer Center, the largest cancer center in the United States, is a consortium made up of seven Harvard University affiliated institutions running about 800 cancer clinical trials per year, in more than a dozen disease areas, with more than 14,000 patients enrolled. And yet until 2000, all of those trials were tracked on paper, and researchers were still grappling with data gaps common to paper records, says Marina Nillni, EDC program manager at Dana-Farber Cancer Institute.

Most of the trials are Phase II trials, with 82% being Phase II, II-III, or III. 84% of the studies are principle investigator-initiated (PII) clinical trials, a number that tripled between 2001 and 2005. These are the most complex trials, Nillni explained, which makes them higher risk. These are also the trials that PIs plan to publish—having their data lost in reams of paper was slowing the publishing process and impeding grants.

When Nillni and her team first started looking at a suitable EDC program, they had a short list of objectives. Nillni wanted a solution that could:
- Eliminate paper case report forms (CRFs);
- Reduce data entry workload through system integration;
- Improve quality of data through up front edit checks;
- Improve turnaround time for study analysis and safety reporting; and
- Increase efficiency by reducing the number of queries to the study team.

With those objectives in mind, the Dana-Farber team came up with a list of 173 functional requirements. For most of 2004—1500 hours—the team investigated options, reviewed RFPs, participated in demos, performed reference site visits and technical assessments, analyzed risks and costs, and finally winnowed the list of EDC options to one: InForm by Phase Forward. It was an “exhaustive process,” Nillni remembered.

After signing the contract in February 2005, the team began the process of bringing the solution in house. “We didn’t want to use a hosted model,” Nillni said. “Given the volume of our studies, that really wasn’t financially a good idea for us.”

Training, hardware and software installation, and library construction took about five months, and in October that year, Dana-Farber launched its first EDC study.

A Few Good Trials

With the huge volume of trials underway at Dana-Farber, EDC implementation could never have been universal. With only a couple of exceptions (a very long-running bone marrow study and a relatively new pediatric acute lymphoblastic leukemia study), no studies were “grandfathered in”, said Nillni. Only new studies were entered into EDC.

Studies were entered into EDC by disease group. Disease groups were chosen preferentially based on the number of paper forms processed in a year, the number of subjects, the number of new trials each year, and the length of those trials. Standard case report forms were developed for disease group as much as possible. Disease programs are most likely to be eligible for EDC if they include multi center studies, long trial duration, and high or fast subject accrual.

Nillni encountered the challenges expected of a very large cancer center with many trials. There was a lack of standardization across (and sometimes within) disease programs. Time was needed from clinical, biostatistic, and technical teams. Large and long-running studies need to reflect changes in EDC over time.

In the four-and-a-half years since the first EDC study went live, Dana-Farber has launched 117 EDC studies including more than 7500 subjects. More than one million paper forms have been or will be saved with the current portfolio and hundreds of phone and email queries have been eliminated. That said, Nillni acknowledges that Dana-Farber still has many more trials that have not been moved to EDC yet.

Asked if she would do it again the same way, Nillni said yes, the research was worth it and the in house model has worked well for Dana-Farber. Indeed, there have been unexpected bonuses. “By going through the process of EDC development—looking at the case report forms and data points and when they need to be collected—protocols became more robust and of a higher quality.”
Under the current global operating environment, biopharmaceutical and medical device companies face far more limited financial resources while time-to-market pressures are intensifying and worldwide clinical research activity is rising steadily. In response, companies are becoming more demanding of their planning and forecasting capabilities and setting lower tolerances for variance between planned and actual performance.

**Trends and Challenges Facing Clinical Development**

Effective study planning is becoming increasingly challenging for trial sponsors. Factors ranging from greater complexity of trial protocols to the increasingly global nature of studies are adding pressure throughout the planning process. In addition, the growing reliance on service providers such as Clinical Research Organizations (CROs) for planning, costing, and conducting clinical studies has helped reduce the planning visibility and control of study sponsors.

The incentive to be more efficient in study planning, however, is increasing along with the pressures. When companies can optimize their study planning, they are able to compress their study planning cycle-times, reduce execution timelines, and reduce costs – while maintaining study feasibility.

**ClearTrial: A New Type of Clinical Software**

ClearTrial software leverages embedded industry intelligence and clinical knowledge to provide quick and accurate “what-if” planning of clinical studies. This Rapid Scenario Planning™ capability lets...

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study sponsors assess multiple clinical development strategies in minutes, and then select the one that best meets their business goals — whether driven by cost, timelines, resources, or a combination.

ClearTrial software delivers a comprehensive set of features to help biopharma-ceutical and medical device companies attain their clinical study planning goals:

- **Embedded global clinical intelligence:** ClearTrial software offers industry-proven algorithms for over 160 therapeutic indications, specific clinical development data from 80 countries, and labor rates for global, regional, and niche CROs, lending speed and accuracy to study planning.

- **Activity-based planning methodology:** By building study plans from the "bottom-up" from more than 140 documented study assumptions, the software ensures that study plans reflect each organization’s unique development goals and methodology.

- **Centralized repository for operational data:** ClearTrial maintains clinical plans in a secure Oracle database, accessible via a secure web connection. Institutional knowledge is thus highly secure, while the system is scalable to any number of users in any part of the globe — all of whom are operating from the same business rules and standards for greater planning consistency.

- **Long-range planning:** The software quickly and easily rolls up study plans into programs and portfolios, providing accurate annual, 3-year, 5-year and even longer-term planning, as well as enabling more effective business development and in-/out-licensing through better visibility to study costs.

- **Rapid time to value:** With its Software-as-a-Service delivery model and easy-to-use interface designed by clinical operations professionals, ClearTrial software can be operational and delivering business value in 48 hours.

**New Approach Offers Important Benefits for Clinical Development Efficiency**
The unique features of ClearTrial software are enabling ClearTrial customers worldwide to conduct more effective study planning, gaining significant benefits:

**Clinical Development**
With visibility to the operational and financial plan for a study, and the ability to quickly and easily create “what-if” scenarios based on clinical assumptions, ClearTrial customers in clinical development are compressing clinical study planning cycle-times from months to weeks while reducing study costs by millions. They are also compressing study execution timelines by optimizing the operational design of the study. And with the embedded clinical intelligence providing warnings when assumptions move out of industry-standard ranges, ClearTrial customers are reducing their study risks at the same time.
Clinical Operations
By providing fast and accurate forecasts of costs, FTE demand, milestone dates and more, ClearTrial software is allowing customers in clinical operations to accelerate delivery of accurate, defensible, and achievable study budgets. They are able to create ballpark study budget plans in less than 30 minutes, and reduce the end-to-end study budgeting process from weeks to hours. In addition, the comprehensive clinical, resource, and cost reports allow them to justify budget and headcount requests, validated against 3rd-party industry intelligence.

Clinical Outsourcing
With the software providing visibility into industry-standard study hours, costs, and resources — combined with intelligence on CRO labor rates — ClearTrial customers in clinical outsourcing are reducing outsourcing cycle-times while increasing their negotiating leverage. They are doing this by quickly generating study RFP specifications based on a minimal number of clinical assumptions, automatically updating RFP's when assumptions change; easily assessing CRO bids and rapidly pinpointing discrepancies; and reducing the disruptive nature and impact of change orders with clear, comprehensive unit price schedules.

5 key characteristics to look for in study planning software

When evaluating clinical study planning software, there are some important attributes that should be on the “must-have” list of any organization. With today’s industry pressures and the advances in software development, there is no reason to settle for less.

Accuracy: Forecasted study costs should be 95-99% accurate when compared with actual study costs.

Speed: Creating comprehensive clinical trial operational plans and detailed study budgets should take minutes rather than days or weeks.

Flexibility: The software should support, out of the box, an organization’s unique business processes and goals, as well as new development methodologies.

Consistency: The same input assumptions should result in the same output every time, from person to person and across functional areas.

Ease of use: Clinical people should be able to easily build study plans and budgets simply by applying their clinical knowledge and expertise, without being technology, financial, or project management experts.

www.cleartrial.com