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SUMMARY

On May 8, 2002, the Silicon Valley World Internet Center convened a Working Group Session entitled "The Challenge for Biotech: Shaping the Future of Clinical Trials." Objectives of this working group:

- To highlight and elucidate the pain points currently faced by biotech companies involved in organizing, managing and assessing clinical trials;
- To address current technology solutions being used in the clinical trial process; and
- To get an in-depth understanding from practitioners on the technologies that could further assist in easing the complexities and improving the efficiency of clinical trials.

Fifteen participants hailed from a distinguished group of companies and organizations involved in the clinical trial process. These included 1747, Abgenix, Berlex Laboratories, Cerus Corporation, Clinimetrics Research Associates, Colby Biomedical Consultants, Fujitsu Software, Iatrix Systems, POINT Biomedical Corporation, as well as several consultants.

The last few years have seen a surge in the number of clinical trials conducted. CenterWatch, the Web-based clinical trials listing service, currently lists over 41,000 active industry- and government-sponsored clinical trials worldwide (www.centerwatch.com). The number of chemical and biological compounds undergoing pre-clinical trials is estimated to be at least a couple of orders of magnitude greater. At the same time, the complexity and expense of bringing a single drug to market has escalated. The Food and Drug Administration (FDA) reports that it takes an average of 8.5 years and about $500 million to bring a single new drug to a patient's bedside. 1747, Inc, a company conducting clinical trials on-line, claims that pharmaceutical companies spend upwards from $20 billion annually on clinical trails. (www.1747.net). The rapid pace of new drug development, combined with the sheer number of compounds undergoing research and testing, is placing tremendous stress on the biotech and pharmaceutical industries.

A BRIEF OVERVIEW OF THE CLINICAL RESEARCH PROCESS

Clinical trials are the accepted method by which new drugs and other medical treatments planned for humans are brought to market. Sometimes referred to as clinical studies or clinical protocols, in essence clinical trials encompass the process of new medicine and treatment evaluation that begins after a company has established that there is good reason to pursue human trials. Typically, development of a new drug begins in the laboratory. The pharmaceutical or biotechnology company undertaking the drug's development conducts extensive research and testing on human cells and animals in order to determine the drug's efficacy and safety profile. Once this efficacy is established for animals, the company will request approval from the FDA to begin testing on human subjects. This request is known as an Investigational New Drug Application (IND). The FDA estimates that only about 0.1 percent, or five in five thousand compounds developed in laboratories, pass pre-clinical trials and advance to FDA-regulated clinical trials.

Most clinical trials span three phases, while drugs approved by the FDA undergo a fourth, post-market phase once the drug has been distributed to the general public. These phases are appropriately known as 'Phase I,' 'Phase II,' etc. Successive phases include a greater number of test subjects. Approval for each successive phase is dependent on the drug or treatment meeting certain specific benchmarks in the preceding phase.

A Phase I study involves between 20 and 100 volunteers. The objective of a Phase I study is to determine a drug or treatment's safety and toxicity by analyzing the way in which it is absorbed, metabolized and excreted by healthy human test subjects. Phase I studies last several months, and approximately 70 percent of drugs approved for clinical trials by the FDA are approved for Phase II studies, based on Phase I results.

Concept & Initial Testing	FDA APPROVAL	Phase I	Phase Ii	Phase III
Animals & Human Cells 0.1% Success		+ 20-100 Humans + Several Months 70% Success	+ 100s Humans + Up to 2 Years 50% Success	+ 1000s Humans + Several Years 70% - 90% Success

Phase II studies focus on testing new drugs and treatments for efficacy and safety. They are typically administered to several hundred patients and may take up to two years to complete. In a Phase II study, not all patients will receive the experimental treatment. In order to establish a control group, some patients will receive a placebo drug. This allows researchers to determine the safety and efficacy of a new drug with a far greater degree of reliability. Approximately 30 percent of drugs approved for clinical trials pass both Phase I and Phase II studies.

Phase III studies involve from several hundred to several thousand patients.   The objective of a Phase III study is to understand the full range of benefits and adverse reactions brought about by the drug, as well as to confirm safety and efficacy parameters established in the first two phases of testing. This phase will typically last a few years, but between 70 percent and 90 percent of drugs that reach this phase complete it successfully.

Once a drug has passed a Phase III study successfully, the FDA considers whether to approve the drug for market. Drugs that are approved typically undergo a fourth phase of studies (sometimes also known as a 'late Phase III' study). The primary objective of a Phase IV study is to verify and monitor the safety and efficacy of an approved drug, as well as to assess the drug's cost effectiveness and its impact on patients' quality of life.

KEY CHALLENGES IN MANAGING CLINICAL TRIALS

Dr. Budd Colby of Colby Medical Consultants kicked off the Session with a discussion of key challenges in managing clinical trials. According to Dr. Colby, the most significant issue is that most biology and medical people do not know very much about IT (Information Technology), and most IT people do not know very much about biology. It is therefore difficult for the people involved in clinical trials to perceive of ways by which technology could assist them. At the same time, it is virtually impossible for technologists to create technologies for the facilitation of clinical trials, a field they know absolutely nothing about. It comes as no surprise, then, that most clinical trial work is still inherently manual. Technology – whether Web-based or otherwise – has been able to play but a minor role.

Recently, this issue has been compounded by the success scientists have achieved in mapping the human genome. This, and similar efforts, are producing immense quantities of data faster than ever before. As a result, the industry's interest in integrating technology into the research process has increased significantly.

Clinical trials constitute the single most critical area of drug development. Trials can last years and cost hundreds of millions of dollars. Consider that a successful drug (not a "blockbuster") generates between $300 million and $400 million in annual sales. Every extra day of trials is, therefore, tantamount to a million dollars in revenues not realized. This creates a very strong return-on-investment (ROI) case for the industry. Every day eliminated from the clinical trial process by virtue of the introduction and integration of more efficient procedures is worth a cool million in sales, and several hundred thousand dollars in margins. Also, considering that millions of dollars are spent on the development of a drug, if a given drug is not going to make it to market, the sooner that fact is discovered, the more cost effective it is for the developer.

According to Dr. Colby, over seventy drugs that have successfully completed Phase III trials are currently under evaluation by the FDA. The number of clinical trials under way is at least eight-fold. The total potential opportunity is, therefore, equivalent to several hundred million dollars *daily*. In order to drive efficiencies into the clinical trial process, the industry needs to get close to people who know how to process data points. The time has come for the pharmaceutical and biotechnology industries to embrace information technology.

WORKING GROUP PROCESS

BRAINSTORMING

Working group participants brainstormed challenges in three key areas:

1. Patient acquisition and case management
2. Data acquisition, storage, retrieval and mining
3. Data analysis

Following the brainstorming session, the challenges were clustered, discussed and prioritized. The following are the results of these efforts, summarized for each of the three areas delineated above. The appendix includes a list of all challenges raised as they relate to these three areas.

Patient Acquisition and Case Management

There was widespread agreement among Working Group participants about the major challenges:

- Patient identification and enrollment
- Recruitment of clinical investigators and competing interests
- Clinical trial setup and management
- Specialty-specific issues
- Globalization of clinical trials

From experience, participants reported that up to 80 percent of clinical trials are delayed because of the difficulties inherent in identifying qualified individuals. Typically, patient identification and enrollment takes longer than anticipated, largely because most researchers overestimate the available population. Further, the process is encumbered by the difficulty inherent in reaching consensus on the characteristics of the necessary test population. Even in the case of life-threatening diseases, when the

FDA allows advanced trials to proceed with hundreds rather than thousands of patients, the process is often bogged down by such issues. One participant commented that trials are sometimes extended by *years* due to the lack of patients. Patient enrollment improves as trials move into later phases.

Another major challenge pertains to clinical trial management. There are a limited number of investigators who can be hired to manage such trials, and they need to be convinced to take on *any* specific clinical protocol. Many investigators are conflicted out of a trial because of their association with competing companies. Investigators also tend to introduce competing protocols into the process, so where multiple investigators are involved, such issues need to be resolved prior to the onset of a trial.

Clinical trial site setup and management can also present a myriad of challenges. The setup process itself may last anywhere from four to six months. This process is lengthy due to communication challenges among the parties involved, legal constraints, business development issues, the difficulties imposed by the need to document anything and everything related to the trial (and to then manage the immense quantities of documentation so produced), and the bureaucracy typical of healthcare organizations.

Patient acquisition and trial management is also a function of the specialty for which a specific clinical trial is relevant. For example, in dermatology, patient acquisition is not considered a problem. One participant reported he had seen over 900 patients recruited in the course of a single month. In oncology, on the other hand, trial complexity is much greater, and several independent scientific reviews, required to be carried out in sequence, can delay efforts by years.

The globalization of the clinical trial process presents an additional and significant challenge. Primarily, other countries require additional layers of regulation and bureaucracy that can further bog down the clinical-trial process. But foreign countries are also concerned that, although they participate in trials, resulting products are not marketed locally once approved. Given that for some diseases the potential American patient pool is simply not adequate, companies are challenged by having no choice but to go abroad in some instances.

Other challenges discussed included the complexity of the trial – the more complex the trial, the more difficult patient acquisition can become -- and patient confidentiality, which is becoming far more prominent as the deadline for HIPAA enforcement approaches.

Finally, participants pointed out that while the knowledge to carry out patient acquisition and clinical trial management efficiently exists in the industry, the process remains extremely inefficient, especially among small companies, although some remarked that the situation was not much better at the large pharmaceuticals. Small companies encounter more issues, however, since they often outsource Phase I studies. As a result, Phase I data may be inconsistent with information gathered in later phases of

study, something that is typically discovered once the drug is already in review by the FDA. When such gaps are encountered, companies are forced to restart trials.

Data Acquisition, Storage, Retrieval and Mining

Working group participants raised a myriad of issues related to data acquisition, storage, retrieval and mining. The main challenges discussed were sample management and remote data capture.

Sample management is a major challenge. Loss of samples is a common occurrence. More complex, however, is the process of ensuring all data elements related to a patient or sample are properly recorded, collected and linked. Many companies have instituted the use of bar codes for this process, but many still use paper labels and plastic tape.

Remote data capture is another major challenge. Improving remote data capture by use of technology is a complex and costly proposition, and participants were not sure that introducing technology into this process would save much time. Further, participants exhibited significant trepidation and concern for the data's reliability, and most would opt to receive paper report forms simultaneously. Many were in favor of using such paper forms to verify system data. Concerns over system costs stem from the need to install such systems at multiple sites and to train staff in their use. The current lack of standardization in the clinical trial process was seen as a key root cause for this dilemma.

Finally, the confidentiality of patient data also presents a major concern as it pertains to the data-capture phase.

One participant commented that (using technology) to reduce data capture to practice (is) a real challenge, to which another participant added that he does not need to know the data, he needs to know the data is there. In response, other participants laid out the benefits inherent in bringing more technology into the process. For example, electronic remote data capture offers clinical trial managers the opportunity to administer trials by remote control. Such technology could provide managers with a confirmation when samples have been pulled or alerts if something is missing. Furthermore, such electronic capture would provide physicians and researchers with data on an ongoing basis, allowing them to intervene proactively and make protocol changes in response to non-adverse events.

Data Analysis

The last area discussed was data analysis. Challenges in this realm are not dissimilar from those encountered in a variety of other industries. The issue of missing data was emphasized. Missing data complicates the analysis, requires sophisticated computational techniques and often causes researchers to go back to trials. Because of the manner by which most data is captured at test sites today, i.e. manually, uploading data can take months. One participant characterized current collection techniques as

"atrocious." Analysis may last several additional months, although some test sites prepare analysis algorithms ahead of time so data can be quickly analyzed. Participants estimated that in this case analysis time may be dramatically reduced.

Even where technology is leveraged for data collection and analysis, the lack of standardization requires that the entire staff typically has to be trained in the use of a new system for every new trial.

CLUSTERING & PRIORITIZATION

Following the group's discussion of the three areas summarized above, participants clustered the challenges under major headings. These included:

A. Trial Administration and Patient Acquisition
B. Remote Data Capture Issues

By way of a democratic vote, participants agreed that "Remote Data Capture Issues" would be the first addressed. The following section summarizes some of the root causes of such issues.

Remote Data Capture Issues – Root Cause Analysis

Why is remote data-capture so elusive in an industry for which it is so well suited? Naomi Fried, general manager and vice president for business development at 1747, Inc., spoke enthusiastically in favor of the immediate adoption of electronic data capture (EDC) systems. Dr. Fried proposed that EDC increases the probability that errors, toxicity and other safety-related issues are identified early on in the process. EDC can also eliminate the need for reviewing paper resource documents and can significantly expedite the analysis of data. Having spent the last several months working with Eli Lilly and the FDA to conduct a Web-based Phase III clinical trial initiative related to a Phase III research effort underway at Lilly, she claims that the FDA is not happy with paper. Nevertheless, EDC is not widely adopted, and few clinical trials are automated in any significant way. The major causes Working Group participants provided for this were the complexity of the task at hand, a lack of necessary resources, politics and culture.

Participants fear that the immense volume of data collected during a typical clinical trial could not be handled appropriately by existing systems. In IT lingo, this concern translates into anxiety over a system's potential to "scale". Some participants were concerned with the resulting shift in the role of the clinical-trial monitor. In essence, clinical monitors will become quality assurance (QA) personnel, overseeing the remote EDC process. Some participants pointed out that, given that clinical monitoring is one of the most expensive line items in clinical trial accounting, this change could lead to significant cost savings, reducing the time monitors must spend on any given trial.

A common objection to almost every technology related project is the lack of necessary resources, both financial and temporal. One participant commented that time is of the essence, and that use of EDC at test sites creates an unnecessary additional burden on staff. Another participant raised a concern that data is entered 24 hours a day, while technical support is not typically provided on a round-the-clock schedule. The concern was that staff might find it necessary to delay data entry until such time as technical support could be reached.

From a financial standpoint the implementation of EDC systems is undoubtedly a costly proposition. Participants were concerned not only with the immediate costs of the system and equipment, but also with the expenses incurred to keep EDC systems humming. Further, the long-term viability of such systems was questioned given that most are marketed by small "single product" startups of the "here today, gone tomorrow" variety. But small biotechnology companies cannot opt to purchase systems from the large, well-established software companies because of the high price of such products. For example, it was noted that Oracle offers a remote EDC module for which it charges $9 per data page with a minimum purchase of 10,000 pages. For most clinical trials, the number of pages of data captured will exceed that minimum several-fold. Given the other costs already incurred in the process, companies cannot afford to spend several hundred thousand dollars more on data capture.

Industry politics were also cited as a root cause for the prevalence of remote data-capture issues. EDC systems would be far less costly if a standard could be agreed upon. Small companies do not have the clout, time or resources to push forward a standard. Large companies, on the other hand, seem to be waiting for one of their competitors to invest in the creation and promotion of a standard.

Perhaps the greatest impediment to adoption of technology in the context of clinical trials – and therefore perhaps the greatest root cause responsible for issues related to remote data capture – is corporate cultural resistance. One participant commented that this resistance is the result of too much familiarity and comfort with the way things have been done for the last 20+ years. The lack of faith in change is exemplified by another participant's remark, made in response to the comment that EDC be adopted immediately. "I do not see it happening in my working life," commented the participant.

What causes such lack of enthusiasm among practitioners? Primarily, industry veterans who have become used to paper-based procedures are concerned with the reliability of data gathered electronically. They expressed concern with the competence of the people entering the data, and a need to employ additional resources to verify and validate the data across from paper-based records – records they advocate the industry continue to collect and keep. They also expressed anxiety over test-site turnover -- the need to train and retrain personnel -- and associated costs. As long as such strong, internal cultural resistance persists, it is difficult to imagine any kind of significant adoption of EDC systems.

THE FUTURE OF CLINICAL TRIALS

Participants, as thought leaders, shared their visions for clinical trials in 2015. One participant suggested the M. D. Anderson clinical management system -- a paper-free environment where all patient data is fed into a single integrated system -- as an example of how systems should function in the future. However, that same participant then commented, "Electronic data entry will never get us away from some documentation."

On the whole, most participants agreed that clinical trials will be run by standardized, integrated systems, accessible anywhere, anytime, from a variety of devices including desktops, personal digital assistants (PDAs), and more advanced technologies such as direct biometric entry. One participant who had recently returned from the annual Drug Information Association (DIA) meeting recalled no shortage of companies developing and marketing similar systems. Most, however, were of the startup variety, and the industry does not seem comfortable placing its bets on such vulnerable players. In the face of cultural resistance, only the future will tell what the true shape of clinical trials will be like in 2015…

APPENDIX I – WHITEBOARD NOTES – CHALLENGES

PATIENT ACQUISITION & CASE MANAGEMENT

- Patient enrollment
- Identify patient population; Trial structures and different populations
- Identify adequate investigators
- Identify high-enrollment sites
- Get sites up and going for trials; Too many "parties" involved and documents to track (lawyers, government, administrative review, scientific review)
- Deal with Competing protocols
- Case management: Contract tracking; Payment to sites and investigators; When based on what?; No consistency among sites
- Do-able trials
- Ensure Patient confidentiality
- Consider patient convenience in enrollment/recruitment
- Patient acquisition: Use niche providers to formalize strategies for patient recruitment (e.g. advertising/incentives)
- Creation and management of adequate databases to facilitate in the identification of candidates for clinical trials
- Non-universality of start-up requirements
- National IRB like EMREC
- Depends on clinical trial phase (I, II, or III)
- Would an 'official' Web site using knowledge management tools help to communicate trial requirements for patients?
- Develop metrics to establish realistic expectations
- "Define" patients: Protocol for identifying patients
- Patient motivation (also a function of phase)
- The need to go "global"; Additional regulations and administrative hurdles
- Unmet clinical needs/small populations
- Sampling invasiveness
- Sampling frequency and its impact on patient accrual and compliance

Additional questions regarding patient acquisition & case management
- How would you increase the population of potential patients (necessary as the number of trials increases)?
- Does good protocol knowledge exist in the public domain?
- Are there any IT-based systems to help in patient acquisition, case management and analysis – if they exist, can they communicate with each other?

DATA ACQUISITION, STORAGE, RETRIEVAL & MINING

- Using complex systems to solve single problems or having a complex implementation of a system makes it difficult to work with
- Patient population changes over time due to the excessive length of trials
- Samples get lost or not pulled
- Get information back to central control
- Splitting samples
- Infrastructure at smaller companies
- Get all the data links pulled and dated: Proper labels; bar codes
- Paper-based records

- Patient compliance
- Safety
- How much of a problem is investigator fraud?
- Monitor trends in missing data
- Manage the acquisition of clinical lab data
- Metrics to monitor protocol adherence / compliance in real time
- Design of data collection instruments (e.g. CRFs)
- Double data entry of paper CRF and electronic forms incurs extra costs - need to move away from paper-based records
- Creating a universally applicable Model T Application: Standards; Security; Confidentiality; Validation; Regulation; Economics
- Lack of sophisticated systems in small companies - How to manage the process efficiently with fewer resources
- Ability to do small phase I to establish pt/pd relationship few patients/many samples
- Site related expenses - site management contributes greatly to cost
- Data acquisition - standardizing source document requirements to substantiate (validate) CRF data
- Remote data capture very costly: Training the site(s) non-technical people; Multiple systems need to be learned
- Lack of standardization for data capture: Screens all different; Equipment all different
- Duplicate data capture is expensive
- Remote Data Entry: data; "data" about "data" needs standardization
- Collect essential data; Need-to-know vs. nice to know
- Know what is missing and know it is there: Know when patient is enrolled; Safety information
- Non-adverse events are key to getting a handle
- For RDE: Direct coded entry, Integration EDI with EMR – Feedback for data integrity and elimination of two-step process
- Is there value in software guidance and data capture devices (i.e. wireless PDA or Tablet PC)?

REMOTE DATA CAPTURE

- Ethical considerations: Who at sites enters data? Or are companies capturing data themselves? Who validates the company's input?
- Support issues 24/7
- Disconnect between who benefits and who does not A need for convergence: Audit trails
- eSolution costs too much (equipment & re-training); Pass on costs to clients so why do it?
- "Incumbents" comfortable with current model of non-electronic data entry
- Source document is your "bible" and needs to be secure
- Need metrics for a paper versus paper-less system: The more complicated the trial, the more $$s saved
- Remote Data Capture: Systems cost being amortized over small base; Large Buy-in Cost & Lack of Adoption (Driven by developers?)
- M. D. Anderson Cancer Center - Electronic charts and database; Subsets of information for clinical trials
- Need acceptance of eRecords by industry in general
- What is the best e-device to capture data in the context of clinical trials?
- Ability to better analyze data; Save time and money, but hard to implement systems
- Need for a "standard" system? (large companies)
- FDA + "reliability" of clean data if use EDC: Who wants to be first?
- Cannot do double data check electronically

- Big Pharma needs cost incentive to proceed with standardization / automation
- FDA needs to reach internal consensus in order for entire industry to move forward

DATA ANALYSIS

- Lack of clean data after study is complete results in delays filing and lost revenue
- How does one repopulate missing data?
- Analysis lags behind even when data is in-house; As a result getting data into the database is a lengthy process
- Administrators making data changes (post trial)
- Pooling data – technology software incompatibilities (Costart – MedDRA)
- Endpoint definition
- Analytical power to see differences between groups
- Agency + market "approval" of objectives
- Getting biotech SMEs the right knowledge and skills; Applies to large companies too
- Companies do not plan long-term (to stay on track for trial)
- Studies/trials becoming static
- Consistency + analysis results in a lack of resources
- Linking clinical data systems (databases) with analysis systems/programs
- Not specifying with enough detail what analysis needs to be performed, e.g. dropouts, rules
- Last minute "massaging" of data
- Real-time analysis to guide patient acquisition goals and requirements per statistical template
- Data analysis as a means to correct deficient protocols/studies
- Parameters to support endpoints

Additional Questions for Data Analysis
- Is there an existing model available for standardization of data capture?
- If remote data capture is good, how could we optimize it or what does it need to do?