



WORKING GROUP

THE FUTURE OF BIOTECH: MANAGING CLINICAL TRIALS IN THE INTERNET ECONOMY

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SUMMARY

On June 18, 2002, the Silicon Valley World Internet Center produced and hosted an Interactive Panel Discussion entitled "*The Future of Biotech: Managing Clinical Trials in the Internet Economy.*" The guiding questions for the panel and the interactive audience were:

- What is the timeline for the “Web-ification” of the management of clinical trials?
- What factors, technological and non-technological, will affect the incorporation of Web-based solutions for clinical trials?

Panelists included Mr. Bob Andreatta, CFO and COO, HopeLink Corporation; Dr. Budd C. Colby, principal, Colby Biomedical Consultants; and Mr. Thomas Tremblay, director of clinical operations, POINT Biomedical Corporation. The discussion was moderated by Dr. Naomi Fried, general manager and vice president for business development, 1747, Inc.

A BRIEF OVERVIEW OF THE CLINICAL RESEARCH PROCESS

(From the Summary of “The Challenge for Biotech: Shaping the Future of Clinical Trials,” May 8, 2002, by Erik Steiner, ©Silicon Valley World Internet Center.)

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 of \$20 billion annually on clinical trials. (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.

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.



Phase II studies focus on testing new drugs and treatments for efficacy. 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. The control group allows researchers to determine the safety and efficacy of a new drug with a far greater degree of reliability than without. 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 study (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.

INTERACTIVE PANEL DISCUSSION OVERVIEW

At the Center's Interactive Panel Discussion on June 18, 2002, several drivers of and challenges to the use of electronic or digitized information in the clinical-trials process were identified. The FDA topped the list as both a driver and a challenge, as did large pharmaceutical companies, or "phasmas." Patient acquisition and the availability of data bases of potential participants; the emerging field of genomics, the science being built around the human genome; competitive pressures between biotech companies; consumer demand; cultural factors of the stakeholders; and technology, both hardware and software, were also identified as drivers and challenges to digitizing clinical trial data.

The timing for adoption of electronic data capture (EDC), and other digitizing of information, was estimated by panel members to be sooner, rather than later. This opinion differs, however, from some members of the May 8, 2002, Working Group who stated that they did not believe they would see mass adoption of EDC in their working careers because of cultural resistance to change. This panel agreed that the changes will occur in steps as the industry chunks out those parts of trials or types of trials which are more suited to facilitation by activities such as EDC, electronic information transfer and patient self reporting. Panel members were unanimous that the pressures currently, and soon to come, on the industry are too great not to adopt more efficient methods of getting new health products to the market quickly.

Traditionally, information on clinical trials is kept in source documents -- anything from a sticky note that the nurse scribbles on to a patient chart to lab reports -- and in a plethora of other forms used for data capture. The volumes of paper resulting from a single trial can fill multiple shipping trailers at a volume of 3,400 cubic feet each. That sea of paper information, by nature, is not easily handled or indexed. There is tremendous expense in worker hours to sift through, store, transport and create reports from data managed in this way. According to panel members, the number of drugs currently in the pipeline are not manageable by the number of people in the system. "And with the dawn of "genomics," panelist and presenter Bob Andreatta of HopeLink Corporation told the group, "drug target numbers are anticipated to increase seven- to 12-fold in the next decades." Members of the panel hope that, by applying technology to the work of clinical trials, drug producers will streamline these processes and be able to better respond to the pressures to bring new drugs to the marketplace.

Data capture, as well as information management, can be aided by the use of technology. Panel and audience members who have conducted trials using EDC praised the ability to manage data in real time and make adjustments accordingly. Data in EDC is more tightly proscribed than with traditional methods of data capture. Erroneous data are rejected by the software, fewer people are required to handle the data, and reports are more easily produced. The stream of data coming into a testing center in

real time may pose an issue for trial managers. “My biggest concern,” said one panel member, “is getting information too quickly and managing that information in real time, making real-time corrections. With more data coming in, you now have a responsibility to deal with the information right now. That does not exist with traditional methods where I might find a piece of paper in my fax machine a few days after the event.” However advantageous the technological approach may be, whatever issues it may present, it is the industry players and stakeholders who will determine the rate of technological adoption.

In the industry, the main players are the FDA, large pharmaceutical companies, mid-size to small biotech companies, contract research organizations (CROs), physicians, hospital staff and patients. Because the pharmaceutical industry is a regulated industry, its regulator, the FDA, has the greatest influence on how trials are conducted and submitted. Traditionally, the FDA has been fragmented and ponderous. This culture has impeded changes in the submission process, and the Agency has stuck fast to old, tried and true ways. But that culture may be changing as the FDA recognizes the precision and mobility of digitized information. Change is in the air at the agency, as a new generation of technology-friendly employees moves up through the ranks. “I am encouraged to see new blood being promoted at the FDA,” commented Dr. Budd Colby of Colby Biomedical Consultants. “The Agency is becoming more and more comfortable with good science and electronic submissions.” Thomas Tremblay of POINT Biomedical Corporation remarked that in recent FDA guidelines, instructions were to digitize all EKGs. “Paper is out-of-date,” he opined. Electronic signatures are also coming into favor with the FDA. Processes are becoming fast and accurate, speeding the flow of communication from the Agency back to the industry, as well as vice versa.

Like the FDA, the large pharmaceutical companies, or “pharmas,” also face a duel role as potential drivers and inhibitors of the adoption of technology and digitization of information in the industry. As a driver, the pharmas could be huge, if they choose to participate in the experiment. They have the money, the resources and the industry muscle to push the technology. They stand to realize increased revenues as products have longer patent lives on the shelf – estimated at a million dollars a day for a moderately performing drug, and increased by a factor of 3 or 4 for a blockbuster. Both large pharmas and biotechs, stand to save money in the development process by switching to EDC. One audience member commented that she had done a trial using traditional methods, and it had cost \$100,000 to conduct. Using EDC in a similar trial, the cost was reduced to \$30,000. Other advantages to the systems were that time was saved putting the report together, edit checks were built into the system and managers were able to monitor problems through a built-in email system. These savings and advantages should appeal to both pharmas and biotechs.

But there are cultural factors in the pharmas that will inhibit EDC and other electronic information adoption. The main reason stated is that many pharmaceutical company executives have

gotten where they are professionally by making conservative decisions and “not making mistakes.” These executives are, therefore, risk averse by training and habit. Any new process could pose a risk of failure. Therefore, they may not try it. Those companies, which are vesting themselves heavily in the new technologies and processes, hope that the economics of the industry and the demand from the public for new products will outweigh this tendency not to try something new. If the pharmas and the FDA do get behind the movement, the timing for change could be very rapid, indeed, especially in certain types of trials.

Investment in EDC by large pharmas, coupled with regulatory requirements imposed by the FDA, could prove a boon to the smaller biotech companies. These companies do not have the resources to invest in developing industry-wide software and hardware standards. They would, however, benefit tremendously by streamlined trials processes. Biotech companies can be heavily invested in one or two drugs that will be their company’s cash-flow, life blood. But, according to comments by members of the May 8 Working Group, they cannot afford the investment in new technologies and processes that are still in the emerging phases. They do not have the resources to move away from their core competency to help the industry develop new processes, and they cannot risk the capital investment. So they continue with business as usual, ready to adopt the new methods once those with deeper pockets have created the industry standards.

Big players in large-population studies are CROs. These are companies whose sole focus is to subcontract with large pharmas to conduct clinical trials. Although CROs may be relatively technologically savvy, they do not have a stake in streamlining the process. According to Dr. Naomi Fried, general manager of 1747, Inc, CROs are vested in and comfortable with the way things work with paper and have little or no financial motivation to change. “They generate most of their revenue by having lots of staff managing all the paper,” said Fried. “They would have to work with computers and learn a new system, and there is no financial benefit to them to do so. If you get rid of the CROs and conduct studies completely on-line, it will save the contracting company 80 percent of both time and cost.”

Although the eventual goal is to have a large proportion of studies on-line, the group agreed that that goal is not achievable until the patient population is entirely computer literate and both hardware and software are more highly advanced. Data entry devices must be developed that are accurate and easy to use. Processes for patients to enter their personal data must be made simple, as they must be for hospital staff and staff at testing centers. But Fried says that as much as 25 percent of trials could be done on-line, and that could happen very quickly. These are trials where no doctor examinations are required, such as trials for incontinence, menopause symptoms and allergies. “We are at a fork in the road,” said Fried. “Seventy-five percent of trials will continue to be conducted by CROs who are not properly motivated,

and adoption of EDC will be very slow. For the other 25 percent of trials where no doctor visits are required, the removal of paper can happen very quickly.”

Another stake-holder group are the physicians. Some doctors are highly versed in the cutting-edge technologies that help them better diagnose and cure patient health problems. Others, especially in private practice or rural areas, may not even own a computer. “No matter how advanced you make the technology,” said Tremblay, “if you give it to a doctor in the country who still uses a rotary-dial telephone, it will not help him.”

While, as a group, doctors are “mainly interested in the patients,” private practitioners could be a boon to the clinical trials process. “In fact,” said Colby, “private-practice physicians are our richest untapped resource to solve our greatest challenge – patient acquisition.” Private practice doctors treat patients who could be involved in trials, but neither the doctors nor the patients are aware the studies are taking place. Panelists suggested that the Web could be used as much for awareness and outreach to this community as for transmission of data. Patient acquisition for clinical trials was identified in the May 8 Working Group as the most difficult hurdle for any given trial. Participants at both the Working Group and the Interactive Panel placed the creation of a large data base of individuals willing to participate in clinical trials at the top of their wish list. Panel members agree, however, that a data base is only as good as it is fresh, and that data would need to be kept up-to-date for a data base to be valuable. Panelists were asked to list some of the features required for such a data base. The responses were:

- 1) Permission and entitlement – the patient would have to be able to give permission for his or her information to be passed on to others, and the patient would be entitled to control his or her information.
- 2) Privacy and security
- 3) The ability to push the information on to others
- 4) Trial information, as well as patient information, would have to be kept fresh.

“The patient needs to know the trial is fresh,” said Tremblay, “and that if she calls to participate, because she has been diagnosed with breast cancer, there is something special to offer her.”

Another group to consider in the change from paper-based to electronic data capture for clinical trials are the hospital and test-center staff. Nurses and technicians are already often overworked. As caregivers, their main interest is relieving the discomfort and protecting the well-being of their patients. To take on a clinical trial in the first place is an added burden. To put in place processes, such as filling out forms and learning a new system on computers, that are outside of their normal procedures would be overly burdensome for them. In order to ease the transition, hospital management needs to make the commitment of time and money necessary to achieve technological change with the least disruption to staff. This would include a commitment to acquire technology, such as personal digital assistants

(PDAs), as well as hardware and software systems, to paid training and to extra staff, if necessary. Currently, most hospitals do not even have a chief information or technology officer, indicating that a huge cultural shift is required.

Any conversation about technology entering a new realm eventually winds its way into discussion of standards. Panelists expressed that proprietary systems have no place in clinical trials. "We need standard applications that everyone uses, just like everyone uses the same suite of office application," said Colby. "We need to see 'Clinical Trials 2002.'" The software also needs to be reliable enough for managers to know that what comes out is what went in. Panelists also agreed with audience members that the patient interfaces need to be very simple to use. Until everyone is computer literate, the telephone is a common instrument for reporting data remotely. Panelists concurred that any trial that uses computers, only, is self-selecting for a sub-group of the population, which could skew socio-economic participation. That patients' personal medical information must be secure is a foregone conclusion. Not only is that security part of the national imagination, but it is legislated by the Health Insurance Portability and Accountability Act (HIPAA). Other emerging technology issues mentioned by the group were signature recognition and voice recognition for patient verification.

Finally, probably the most influential stakeholders in the adoption of new technologies to speed up the development of new drugs are the public. "Fifty percent of the public out there on the Web researching health conditions are suffering from those conditions," said Colby. "They are looking for help." Consumers are living longer and looking for new solutions to old problems. This implies a tremendous market for new drugs. Adding to this is the fact that in the next 3 years the largest generation in the country, the Baby Boomers, will begin to reach the age of 60. Cancer begins to strike with its greatest ferocity when people reach their sixties, which means there will be a huge demand, as well as economic benefit, for providing new cancer drugs.

But in the end, the industry, itself, needs to identify exactly how it will go forth with the convergence of science and technology to speed new cures, pain relievers and symptom reducers to market. 1747, Inc. currently conducts certain types of trials entirely on-line and with no paper. The University of Texas' M.D. Anderson Cancer Center conducts research and trials using digital data entry and capture. Strides have been made, but there is a long way to go. "The industry needs to identify which pieces can go forward," said Tremblay. "It will not happen all at once." But it is a beginning.