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Keywords: *clinical trials, EDC, Web-based technology, process change, site investigators, subject safety*

eClinical trials: The future is now

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Date received (in revised form): 30th May, 2002

Abstract

Clinical trial conduct today requires improvements in efficiency, accuracy and subject safety. These benefits are available as the industry makes clinical trial process changes through Web-based technology.

INTRODUCTION

The clinical trials industry provides the human clinical research process for new product development in the pharmaceutical, biotechnology and medical device industries. According to Forrester,[1] the clinical trials industry was a US$50bn industry in 2000, experiencing double-digit growth since 1995. The growth of this industry is expected to continue at a rapid rate owing to the increased pace of new drug compound and genomic discoveries. Figure 1 provides information on the development life cycle of a new drug compound, illustrating the timeline of discovery, research and submission. Issues today include increased development creating a bottleneck at clinical research, and the need to reduce the research cycle. A major problem with the current development cycle is the limited time a sponsor maintains a patent-protected revenue stream from an approved product. A major area of concern is the ability of the clinical trials industry to keep pace with the discovery growth.

Many industries have transformed their business practices over the past 20 years because of technology enhancements. Enhancements included larger and much more powerful computers, the proliferation of smaller, yet powerful and flexible personal computers, and the development of business software taking advantage of these gains in computing power and flexibility. One industry where the technology gains have not produced

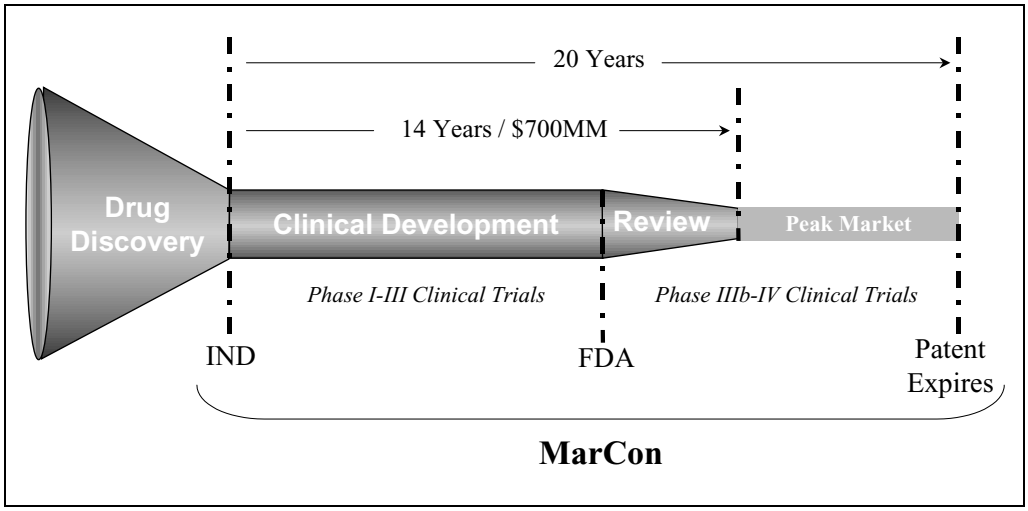

Figure 1: Market time and cost pressures. IND – investigational new drug (application), FDA – US Food and Drug Administration

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as much as expected is the clinical trials industry. A major reason for the lesser gains is the heavy reliance on paper-driven processes required to meet regulatory requirements for clinical research. The end result is that clinical research today lags behind most industries in taking advantage of technology gains. To become more efficient and to meet the growing clinical research demand described above, the industry must take advantage of better technology-driven solutions becoming available now.

eClinical Trials (eCT) refers to the result from a transformation of the clinical trials industry from a slow, inefficient paper-driven industry to a rapid deployment, real-time conduct, efficient industry driven by technology-enabled clinical processes.

Goals:
- **identify clinical trials issues**
- **document solutions**

The goal of this paper is to address the issues inherent in current clinical trials conduct and to document contemporary solutions that can lead to major gains in research efficiency, accuracy and subject safety. The paper will focus on three major areas – clinical research problem areas ready for improvement through re-engineered processes, technology advancements that will enable process changes, and needed thought process thought change required for Return on Investment (ROI) benefits to accrue in the new world of clinical research.

CLINICAL RESEARCH PROCESSES

There are five problem areas that many would agree exist in the clinical trials industry. Solving these problems would go a long way towards bringing the enhancements expected in this industry. We believe all five problems can be greatly improved through technology enabled re-engineered processes.

Research issues:
- **decentralisation**
- **reliance on paper**
- **lack of process coordination**
- **investigator discontent**
- **subject safety**

The five problem areas are (1) decentralised information, (2) heavy reliance and focus on paper, (3) lack of coordination of multiple clinical trial processes, (4) disconnection with biomedical investigators who conduct the actual study protocols and (5) subject safety. Below we address these five areas and opportunities for improving each area.

Centralise information

Clinical trials begin with the creation of a detailed scientific protocol, explaining clearly the research goal and the science to be conducted to achieve the goal. After creation of this detailed plan, the sponsor then distributes the protocol to all study constituents – investigator sites, Institutional Review Board (IRB), monitors, external laboratories and any other constituents participating in the trial. From this point forward, study information accrues in many locations in a very distributed manner. The result is that the sponsor and principal investigators (PIs) responsible for study conduct do not have the information needed to keep the study on track. For example, it is well documented that 80 per cent of clinical trials do not meet their enrolment targets,[2] they typically take 3–6 months longer than expected to complete subject enrolment. One reason is that the sponsor does not have access to up-to-date enrolment activity at its investigator sites.

eCTs will provide all clinical trial information in a centralised database in real time. In this environment, sponsors will have access to online reports indicating enrolment figures in real-time, reported by investigator sites. The result is the sponsor will have current information about enrolment and can move more quickly to motivate, or replace, sites not meeting their enrolment schedule. This feature alone can reduce the length of clinical trials by 3–12 months by better ensuring enrolment remains on schedule. Similarly, the IRB, monitors, investigators and all study constituents can have worldwide access to their needed study information in real-time from the centralised database to ensure better study conduct.

Reduce reliance on paper

The capture of study subject data into a computerised database by the medical investigator is called electronic data

capture (EDC). This process seems misnamed because it is actually much more manual in nature than electronic. Clinical trials typically involve first recording all subject data on paper case report forms (CRFs). Data from completed CRFs are then entered into a personal computer, usually by investigator staff at the site. Capturing data in this manner leads to the original CRFs being the 'paper-based source documents' for the clinical trial. The defined source documents are quite important for a clinical trial as they drive the regulatory process regarding final accurate data. Much time and effort are involved in following the paper trail of getting complete and correct data from the paper CRFs into the study's computerised database.

Need for 'electronic source documents'

eCTs will use 'electronic source documents' (ESDs) which involve entering the subject data directly onto an electronic CRF on a computer. Web-based software checks the data immediately for completeness, for meeting study eligibility criteria, and checking within reasonable ranges for numerical measurements. CRFs satisfying these criteria have their data immediately stored in the central computerised database. The end result is that entered data are essentially complete and valid, which greatly reduces the monitoring and follow-up work required to ensure a complete and clean database.

Reduce monitor queries

Improve investigator performance

A query is a request by a monitor to an investigator about a specific data element collected on a subject. The monitor would have a question about the data element and the investigator is expected to correct an error or acknowledge the data element is correct. A typical clinical trial may generate thousands of queries.[3] Early reports from eCTs indicate the potential for a major reduction in queries,[4] one reporting as much as 86 per cent reduction in the number of queries.[5]

Coordinate multiple processes

Efficiency gains from coordinated processes

There are numerous processes involved in the conduct of a clinical trial. Some of those processes include EDC, randomisation, eligibility determination, medication dispensing or device delivery, IRB services, adverse event (AE) management and reporting, site financial reimbursement, external laboratory participation, study training and others. These processes are accessed and used by various constituents of the clinical trial such as the sponsor, sites, IRB and monitors. Figure 2 provides a view of the integration of constituents and multiple processes through the centralised database. In current clinical trials, these processes operate independently and in a distributed manner.

In eCTs, information from all these processes is stored centrally and made available to appropriate study constituents through a secure permission system. Further, successful eligibility leads to immediate and automated randomisation of the subject, followed by immediate electronic medication dispensing, if appropriate. Submitted AEs can generate immediate e-mail notification to study safety officials leading to faster and more interactive resolution and then electronic submission to the FDA. These are examples of more study efficiency gains from the coordination of multiple study processes and integrated involvement of all study constituents.

Enhance investigator involvement

Successful clinical trial conduct requires the participation of medical investigators – usually a physician, nurses and possibly physician assistants in the practice. Physicians are reimbursed for their participation and that of their staff in a clinical trial. A problem in clinical research is the low participation of physician practices in clinical trials. A major reason for this low participation is that physicians and their staffs are not used efficiently. They are asked to use proprietary hardware and software specific to the clinical trial, perform workflow out of the normal office routine, and subject

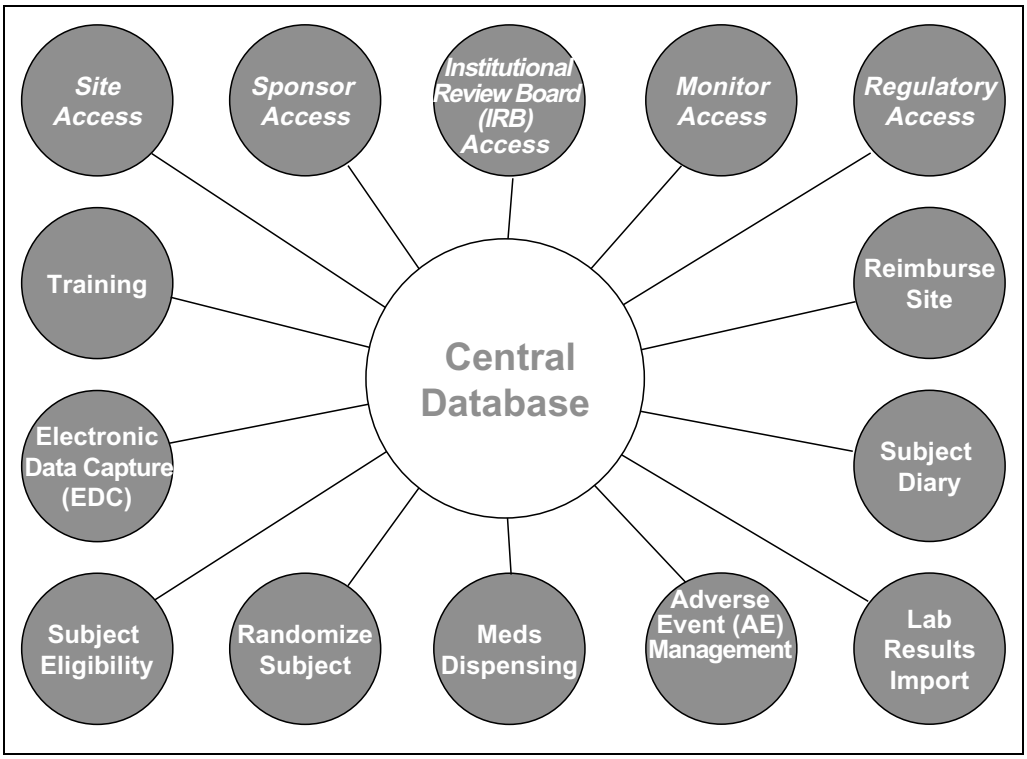

Figure 2: Integrated constituents and research processes

themselves to extensive monitoring of their work.

Improve investigator training

eCTs improve each of the investigator problem areas. The only computing environment required for any study is a contemporary computer and browser, something easily available in most medical practices today. No proprietary hardware and software are required, greatly simplifying a site's computing needs and system training. Study training on the protocol, good clinical practice (GCP), subject informed consent, and any other area of sponsor interest, can be completed in an online training session. Further, the system can document successfully completed training for each study investigator, which should enhance study conduct. An additional benefit is to reduce the need for expensive investigator meetings that generally require travel by all investigators to a central location for a 2–4 day meeting. Unfortunately, after these meetings, sponsors are still unsure of the level of training achieved. Another example is the process of randomisation, which is the non-medical statistical method of assigning an eligible subject to their study treatment. The randomisation process currently takes a nurse 15–30 minutes on the telephone with an interactive voice recognition system (IVRS) per eligible subject and requires monitoring. In an eCT, randomisation is performed in seconds electronically with the result automatically stored in the database. The result for the investigator is no work to randomise their subjects and, hence, nothing to be monitored. Eliminating randomisation from an investigator responsibility is an example of improved work flow for an investigator site. The result is an investigator focuses more on medicine and science, and spends less time on study administration and bureaucracy. With enhancements for the site as presented here, we believe more medical professionals will want to participate in clinical trials both for the additional revenue and the perception to their patients of being on the cutting edge of medicine.

Investigator focuses on medicine and science

Electronic randomisation

Forrester[1] noted that a major myth is that investigators are opposed to EDC.

Forrester found 'physician investigators open to on-site data entry, in part because faster query resolution translates into shorter monitoring visits, presently a source of disruption to the office'.

Improve subject safety

Recent high-profile safety issues at leading research universities as University of Pennsylvania, Duke, Oklahoma and Johns Hopkins indicate the need for better protection of subjects who agree to participate in clinical research.[6] The federal government Office of Human Research Protection (OHRP) oversees subject protection and the activities of IRBs and is clearly interested in improving safety. The decentralised nature of current clinical trials makes it difficult for safety officials to properly monitor safety.

Online IRB

In eCTs, the IRB is online and can directly control investigator access. An investigator cannot begin study participation until the IRB electronically approves the participation. The IRB can also remove an investigator's access to participate if any concern of misconduct is suspected. Annual renewal of sites and other IRB activities can be managed online and all its needed information is managed in the centralised database.

Systems interoperate using standard protocols

Also, when a serious AE is submitted electronically, instant e-mail notification of the AE can be sent to all identified study safety officials. The result is a more timely and automated response to the AE to gather needed information and eventually complete the AE resolution. The completed AE can then also be submitted electronically to the FDA. The result is faster gathering of information and resolution of the AE, leading to enhanced subject safety and replacing this primarily paper process with Web-enabled technology and a totally electronic process.

Results

Process improvements needed for technology benefits

eCTs can have a major positive impact on the conduct of biomedical clinical trials. The key to the improvement is the acknowledgement of needed process improvements and the use of Web-enabled technology to achieve these process improvements. Observable results will be an improved monitoring system, improved regulatory environment, and an overall more efficient, accurate and safe clinical trials system.

TECHNOLOGY

To move from existing processes to eCTs will require a technology infrastructure capable of supporting a diverse group of users and requirements. The public global Internet provides a ready-made communication system reaching the participants and, if carefully exploited, providing the reliability, throughput and security required to conduct eCTs on a global basis.

Systems deployed on the Internet can interoperate using standard protocols. Web browsers are readily available, providing a pre-existing and suitable platform for all participants in eCTs. Hypertext Mark-up Language (HTML), Secure Socket Layer (SSL), Hypertext Transport Protocol (HTTP), Simple Mail Transport Protocol (SMTP) and Transmission Control Protocol/Internet Protocol (TCP/IP) provide common worldwide standards for browser-based communication with Internet systems and their users.

Servers deployed on the Internet can provide services for eCTs as shown in Figure 3. Constituents accessing eCT processes can be located anywhere in the world without regard to server location. Servers can be physically secured and secured from the routine threats of the Internet.

Server-based systems to facilitate eCTs must meet several basic requirements. Such systems must be flexible to meet the needs of investigators and sponsors. Systems must scale up to provide services and integration on a world-scale. Site investigators must find the systems beneficial to their work to assist in their subject recruitment and execution of the clinical protocols. Sponsors must find the systems achieve their goals with respect to

Figure 3 Servers on the Internet can provide worldwide services for eCTs (note: O denotes location of servers)

regulatory requirements. Systems must adhere to industry and international standards for data representation to insure interoperability and low cost for implementation and operation.

Flexibility

Systems must support many varied processes

Systems must be flexible

To be successful, an eCT services platform must be capable of supporting a wide variety of processes. From the straightforward display and storage of form-oriented data in EDC to real-time interfaces to diverse systems such as laboratory, imaging and financial, a wide range of capabilities configurable to meet requirements must be available. The needs of trial participants vary greatly, as do the requirements of the different phases of clinical research.

Phase I clinical trials require very rapid start-up. A system must be able to replicate an existing study and provide study editing capability. Reusable study components, including workflows, reports and forms, can provide a tool kit for rapid assembly and start-up of new trials.

Phase I, II and III trials must meet strict regulatory requirements while providing flexible configurations to meet sponsor and investigator requirements. The work to be performed varies by therapeutic area. Systems must be capable of handling a wide variety of data types and input sources, including on-screen forms, locally deployed devices and feeds from central services such as laboratory and pharmacy.

Finally, systems must be flexible to adapt to new technology, new opportunities for data exchange and integration, and new and enhanced data representation standards. Systems designed as recently as five years ago may not be capable of achieving the flexibility required for support of eCTs.

Scale

System must scale

As a sponsor's eCT adoption grows, the technology must be able to scale to meet increasing demands for storage, throughput and processing. With care in design and execution, modern systems scale well. Databases such as Oracle and IBM's dB2 are capable of handling millions of forms, as well as practically unlimited numbers of sites, studies and users. Middleware frameworks such as Java 2 Enterprise Edition (J2EE) have been proven to support the largest worldwide commercial activities in banking, manufacturing and telecommunication. These solutions scale to multiple servers, so that eCT support can easily grow. No slowdown due to increased numbers of users should be

experienced. With a proper architecture, more resources can be added to support additional activity. Additional disk space can be added to increase storage without changing the eCT software. Additional servers can be added to increase throughput. Additional bandwidth can be added to alleviate constraints caused by network congestion. These improvements can be made without changing the software. The software itself has no scaling limits. A well-deployed eCT system can scale up to meet the needs of the global clinical research community.

Investigators need motivation to recruit subjects and execute protocols

Site acceptance

An eCT system must achieve wide site acceptance. The success of a clinical research programme depends on the ability of the sites to recruit subjects and execute study protocols. Sites need simple, one might say obvious, systems that fit well in their clinical workflow. Flexible systems can be configured to provide the sites with research workflows consistent with their practice and the protocol. eCT systems should provide all study materials on-line as well as on-line context-sensitive guidance. For many sites, use of the eCT system will occur once or twice per day. Such infrequent use in an otherwise very hectic clinical environment requires a user interface that is trivial to master. Response time must be good since this directly relates to site satisfaction and acceptance.

By eliminating complex manual processes and providing an intuitive, organised approach to all the materials and workflows a site requires for participating in a clinical trial, an eCT system can achieve high levels of site satisfaction and efficiency.

Systems must improve processes and reduce cost

Sponsor acceptance

An eCT system must meet strict regulatory requirements while delivering measurable process improvement and cost reduction. Systems and operation of systems must be validated to meet FDA and ICH guidelines.

In most cases, the sponsor will have existing systems that must be interfaced to the eCT system to provide investment protection, transition capability and access to additional sponsor processes. The eCT system must provide clear application programming interfaces (APIs) to construct these interfaces. This permits the sponsor to follow a 'best of breed' information technology solution, using native eCT system components when appropriate and combining the eCT system with other systems that may provide a competitive advantage (see Figure 4).

The application service provider (ASP) relationship to the eCT system greatly simplifies the sponsor's role. The ASP hosts the eCT system, providing all related IT resources – computing, storage and bandwidth – as well as all IT support – system administration, security, help desk, backup, maintenance. The sponsor operates existing participating services as desired.

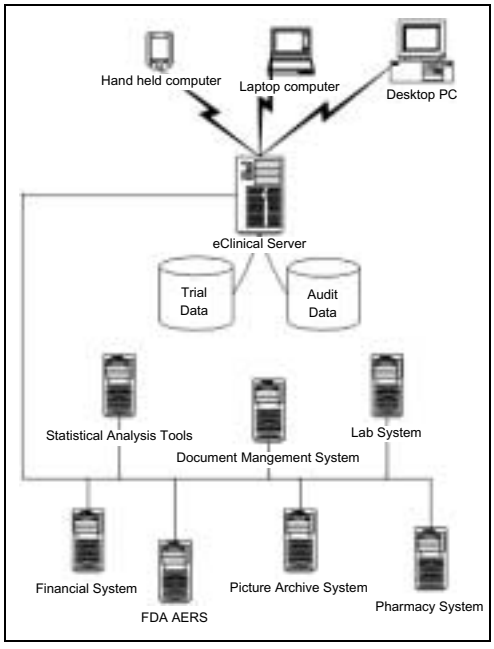

Figure 4 A typical API bringing together sponsor and eCT system components, resulting in a 'best of breed' IT solution

Systems must meet industry and regulatory standards

Standards

eCT systems must conform to standards. In addition to the aforementioned Internet Standards, an eCT system must meet industry and regulatory standards. Controlled vocabulary standards such as MedDra and UMLS must be supported as well as data representation standards such as Extensible Markup Language (XML), for creating data exchange standards, the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM) for representing clinical trials and their data, and Health Level 7 (HL7) for representing clinical values. All standards must be used to ensure high levels of interoperability and reuse, leading to shorter cycle times and lower cost.

Regulatory requirements provide an additional set of standards that must meet compliance with 21 CFR Part 11, HIPPA (Health Insurance Portability and Accountability Act) requirements, requirements of the Office for Human Research Protection (OHRP) as well as international and country specific requirements. Participation in the FDA Adverse Event Reporting System (AERS) will also be required. These regulations are constantly being refined and reinterpreted. New regulations must be anticipated by the clinical trials industry. The need for compliance with standards requires constant refinement of the eCT system.

Results

By addressing the needs of flexibility, scale, site and sponsor acceptance, and conformance with standards, an eCT system provides a platform for process improvement. By executing improved processes across the clinical research enterprise, using a centralised, real-time, Internet-based eCT system, sponsors and sites can achieve tremendous gains in efficiency, accuracy and patient safety while simultaneously lowering trial duration, time to database lock and cost of study.

Gains in:
- **efficiency**
- **accuracy**
- **subject safety**

Reductions in:
- **trial duration**
- **time to database lock**
- **cost**

More information on clinical trial process enhancements through Web-enabled technology is available.[7]

BUSINESS PROCESSES

The value proposition for eCTs can be described in three areas of the business process. Those three areas are (1) in direct operational savings, (2) making more timely go/no go decisions on new products being tested and (3) expanding the peak market opportunity. Each of these areas and their opportunities for improvement are discussed below.

Direct operational savings

Operational savings occur in two major areas – improved end user productivity and in reduction in use of paper for the trial. All constituents of a clinical trial – the sponsor, investigators, monitors, IRB personnel and product supply personnel – can be more efficient in an eCT. For example, biomedical investigators at the sites (physicians, nurses, etc.) all become more efficient in their roles based on the changes in their functions as described earlier. Monitors have a major role in overseeing all site conduct in the clinical trial. An eCT makes the monitoring job more efficient through real-time monitoring and the transition from monitoring paper-based information to electronic information. As mentioned earlier, queries are substantially reduced in an eCT, resulting in a reduction of monitoring effort required in an eCT. Similar efficiency gains can be achieved for other constituents in the eCT.

The cost of printing and managing all the paper documents in a clinical trial is large. An eCT essentially eliminates the need for all these paper documents through the use of electronic source documents described earlier. The main paper requirement would be if a sponsor wanted site investigators to print completed CRFs to store as part of the study subject's medical record.

Timely go/no go decision making

In pharmaceutical research, only a small percentage of compounds studied complete the research process and make it to market. It would be helpful to the

pharmaceutical industry to be able to identify ineffective compounds more quickly, and be able to stop their research more quickly. By having real-time access to all research information, the sponsor is better able to identify failed compounds and pull the plug on their research spending, resulting in reduced savings that can be allocated to more promising compounds in the pipeline.

Expanded peak market opportunity

Business operation needs restructuring

Figure 1 illustrates the 20-year timeline of a typical drug compound, illustrating the lengthy research process and the limited peak market revenue under patent. A goal of the industry is to reduce the product development timeline, resulting in enhanced patent-protected sales opportunity. Many people believe that the cycle times for clinical trials can be shortened on both their front and back ends. Sponsors have the opportunity to keep clinical trial enrolment on schedule based on worldwide real-time access to precise enrolment information. Such information can reduce the start-up times of clinical trials by 3–12 months. Similarly, by achieving cleaner data more quickly through the use of ESDs, sponsors can shave 3–6 months from the data clean-up stage at the end of the clinical trial and achieve a locked database for analysis more quickly. Further, the reduced time to conduct the research and better organised electronic information can lead to faster regulatory approval as well. Extending these savings across all the clinical trials in a compound's development has the potential to increase the peak market opportunity by about two years, providing substantial additional revenue for the product during its patent protected lifetime.

Business benefits will accrue

Business decision to redesign processes

One additional note is that the sponsors of clinical trials must be willing to restructure their organisations around the new model for clinical trial conduct. One problem to date for sponsors in the acceptance of eCTs is the perceived lack of efficiency gains expected. The primary reason is that early vendors and sponsors of more electronic clinical trials have not changed processes but, instead, have continued the standard conduct of clinical trials. Information collected through the usual, old, processes is transferred over the Internet. The result is 'inefficient old processes + new technology = inefficient new processes'. Achieving the efficiency, accuracy and safety gains offered by eCTs requires some fundamental changes in the conduct of clinical trials and the organisational management of their clinical research programme. The business operation needs to be restructured from a department-based organisation to a process-based organisation. Teams need to be organised around the new model for research conduct and be able to respond quickly to clinical trial needs as they are more quickly identified in this new world of clinical trial conduct. The result will be a more coordinated team approach to the clinical trial process, achieving the efficiency gains expected of this new operational model.

Results

There are numerous valuable benefits that will accrue to sponsors in the new world of eCTs. Benefits include reduced cost of clinical trials conduct through productivity gains and reduction in paper use, more timely go/no go decisions on compounds being evaluated, an expanded patent protected peak market opportunity, and improved efficiency, accuracy and subject safety. These benefits are for the sponsor, all clinical trial constituents and, ultimately, for the general public through more efficacious products reaching the market sooner.

SUMMARY

The conduct of clinical trials has remained largely unchanged for many years. Technology gains brought to other industries have eluded the clinical trials market to date. A main reason for this hold back has been the industry's conservative nature and regulatory requirements. Given the continued

double-digit growth expected in the research pipeline of the clinical trials industry[1] and the FDA goal of becoming electronic by the end of 2002, the clinical trials industry seems motivated to improve its efficiency to keep up with its research needs. This paper has summarised the needs and opportunities for the clinical trials industry to become more electronic in its operations. By doing so will improve the efficiency and accuracy of clinical trials conduct and enhance subject safety creating an important win–win–win proposition for this important industry.

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