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MARKET ANALYSIS

Clinical Trial Automation and Data Management Solutions

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IDC OPINION

Efforts to answer industry demands for solutions that enable the time- and cost-saving automation of clinical trials have resulted in a wide array of vendor solutions. The potential for these solutions is enormous, but significant hurdles accompany their implementation and acceptance. IDC has indicated the presence of a leading vendor or vendors in spaces where a leader exists, but in less mature segments, key players are identified without the designation of a leader. This document initiates IDC's coverage of the clinical trial application space, and the taxonomy developed herein will be implemented in subsequent publications. This document:

- Characterizes the areas of opportunity and identifies challenges for vendors
- Provides a clear and concise explanation of the regulatory and industry environment
- Presents a definitive segmentation of the market on the basis of functionality produced by vendors and offers a look at the top vendors producing applications in each functional space

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TABLE OF CONTENTS

LIST OF TABLES

IN THIS STUDY

Methodology

This IDC study reflects an extensive survey of industry publications, interviews, and presentations on the topics and applications covered. The result of this research and subsequent analysis is a definitive segmentation of the universe of clinical trial management applications on the basis of functionality provided by vendors. This document provides brief descriptions of the top vendors producing applications in each functional space. IDC has indicated the presence of a leading vendor or vendors in spaces where a leader exists, but in less mature segments, key players are identified without the designation of a leader. Analyst insight has been incorporated into the coverage as appropriate.

SITUATION OVERVIEW

Intelligence

Market Group Overview

In the management of clinical trials, companies are slow to adopt technology because of the complex regulatory environment and a history of inherently conservative practices. This is undoubtedly due in part to the operational burden, financial expense, and uncertainty of complying with regulatory requirements. Nonetheless, over the last few years, fueled by available software innovations (often imported from other industry verticals) and an increasingly supportive Food and Drug Administration (FDA), industry attempts to harness recent advances in technology have accelerated.

Solution providers have taken different approaches in providing software tools designed to accelerate the clinical trial process, including:

- **Single-point solutions.** Single-point solutions are directed at acknowledged, singular bottlenecks in information or process flow.
- **Multipoint solutions.** Multipoint solutions are directed at several areas, but may be separable to address a single point.
- **Integrated solutions.** These are enterprise-level solutions directed to more efficiently move information through the organization.

In this study, we examine the clinical trials IT environment, the business factors driving change, and the solutions being presented and speculate on the future for clinical tool providers. This document will provide a clinical trial IT market definition and describe the spectrum of applications and the leading vendors that service the clinical trial market.

Current Situation in Drug Development

The numbers are well-known: In its *Outlook 2003* report published in November 2003, the Tufts Center for the Study of Drug Development (CSDD) reported that the time required for clinical and approval phases for new drugs averaged 6.9 years, while the average cost to develop and win market approval for a new drug was $802 million.

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Key factors that are affecting the global drug development environment include:

- Increasing R&D spending and falling R&D productivity
- Past "blockbusters" (revenue of >$1 billion per year) losing patent protection
- The increasing difficulty of finding new blockbusters because most common diseases already have successful medical treatment options
- Increasing global drug pricing pressure
- Increasing requirement of pharmacoeconomic justification for new products

Productivity levels in drug development, as measured by the numbers of new drugs and biologicals reaching the market, have not increased in recent years, despite dramatic increases in R&D spending (Kaitin, Kenneth; Tufts CSDD Approved NCE Database, data presented February 12, 2004). Most of this spending has been on technology related to advances in high-throughput compound screening and in vitro testing. It remains to be seen if these R&D advancements have improved decision making for companies at the early stages of compound development. Although biologicals represent a new source of revenue for many pharma companies, they are not making up for the productivity slowdown. Although numbers vary depending on the source, to get one drug to market, it takes between 5 (PhRMA) and 50 (Bell, Angus; Quintiles, 2002) drugs entered into clinical studies, and for every 5 drugs entering clinical studies, between 5,000–10,000 drug candidates must be evaluated in preclinical studies.

About $70 billion worth of drug sales will lose patent protection over the next few years.

About $70 billion worth of drug sales will lose patent protection over the next few years. Accelerating the drug development process allows companies to maximize revenue prior to products losing patent protection, and the clinical trial period is the focus of acceleration efforts. Clinical trials are the most time- and cost-intensive phase of development (Kaitin, Kenneth; Tufts CSDD), and companies are intent on accelerating the trials, data collection, and analysis with technology. It is more important than ever for drug companies to perform the right trials at the right time to answer the questions posed by the FDA about new products. Clinical trials are the largest single cost center (over $9 billion) in the estimated $45 billion annual pharmaceutical R&D budget.

Global pricing pressures have also become an issue in drug development, as evidenced by FDA Commissioner Mark McClellan's December 2003 speech to the European Federation for Pharmaceutical Sciences (see **www.fda.gov/oc/speeches/2003/eufeps1208.html**). McClellan noted that there is increasing pressure to globalize drug costs, and he proposed solutions, including addressing questions of patent protection and exclusivity periods, sharing

development costs, developing international harmonization of approval requirements, and creating price protection for consumers. All of these solutions have the potential to affect the flow of dollars into the drug development process and demand innovation. Although McClellan appears to be leaving the FDA, it has been indicated that his initiatives will continue, and it is expected that he will continue to affect FDA policy from his post at the U.S. Department of Health and Human Services (HHS).

The Regulatory Environment

Global Regulatory Environment

The regulatory environment for clinical trials is complex. This discussion is limited to the impact of regulations on electronic data collection and submission. The three global "regions" that can be defined for drug sales are the United States, Europe, and Japan. These three regions account for 82% of global drug sales, and over half are in the United States (Kaitin, Kenneth; Tufts CSDD Approved NCE Database, data presented February 12, 2004; IMS Health Global Pharma Forecasts, 2001).

In the United States, the main regulatory body is the FDA. Security of clinical data such as preserving the confidentiality of medical records for trial subjects is also governed by the Health Insurance Portability and Accountability Act (HIPAA), which is administered by the Centers for Medicare and Medicaid Services (CMS). Both CMS and the FDA are part of HHS.

In European Union (EU) member countries, the governing body that oversees clinical trials is the Commission of the European Community's (CEC's) European Agency for Evaluation of Medicinal Products (EMEA). The EMEA was formed in 1993, but its ability to regulate is complicated by previous processes within EU member states and the ever-expanding size of the EU. Japan's regulatory body overseeing drug approval is the Ministry of Health, Labor, and Welfare (MHLW).

These three regions are participants in the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), which has developed a common technical document (CTD) and electronic CTD (eCTD) that are designed to harmonize approval requirements in the three regions. The eCTD creates a common process for stability and toxicity testing, including safety and adverse event data, thus facilitating a common adverse event database accessed by the three regions. The eCTD provides a common format for a new drug application (NDA) across countries. What it does not do is consolidate the clinical content of the application so each region still has its own clinical and administrative content. Additionally, some regions require pharmacoeconomic studies prior to approval. Japan and Europe are mandating the CTD as of July 1, 2003. The CTD is "recommended" by the FDA and was published in the Federal Register; in 2003, 64 NDAs were submitted by 34 companies in CTD format (**www.cder.gov**).

Globally, the United States is usually the starting point for drug companies commencing clinical development. The United States has a strong infrastructure for conducting clinical trials; the modernization of the FDA has led to a strong clinical focus, as it takes the lead in establishing guidelines for proving the efficacy and safety of new compounds. Clinical development in Japan is particularly difficult, as a premature CTD implementation represented a dramatic change to the Japanese

clinical trial process, and it has been nearly impossible for companies to staff and perform trial requirements, hindering trials and drug approvals. The European focus is strictly regulatory, and reviewers are often nonclinical practitioners with little input into clinical processes.

Clinical Development

Regulatory requirements for drug development companies include clinical trials to determine the proper dose of a drug and evaluate product efficacy. The FDA's clinical trial process identifies four clinical trial phases that use facilitating software (see Table 1).

TABLE 1

Phase of Clinical Trials

Phase	Description	FDA Role
I	Phase I includes safety studies in small numbers of healthy volunteers with placebo control. All clinical trials require submission of an investigational new drug (IND) application to the FDA.	The IND application is submitted for ethical evaluation of trial protocol. There is a 30-day evaluation period, after which time, an IND is assumed to be approved.
II	Phase II includes dosing studies to determine the dose/response curve, the appropriate dose(s) to use in subsequent trials, and the maximum tolerable dose (MTD). The studies are small, with diseased patients.	Post-phase II meeting with the FDA is critical to determining course of Phase III trials and the submission of the NDA. No time limit is placed on FDA review of Phase II data.
III	Phase III includes an effectiveness study in a large number of patients. Usually, a "pivotal" trial is required that definitively proves the drug's efficacy.	The NDA is submitted at conclusion of Phase III. There is no time limit, and the FDA may ask for more information/ additional trials if the application is not conclusive.
IV	Phase IV trials may include: • Postmarketing studies following marketing approval to continue to prove efficacy and safety for orphan drugs or life-threatening conditions. • Pharmacoeconomic trials proving the cost-effectiveness of a treatment to government or private payers. • Any trial initiated after NDA submission.	The NDA is under review or conditional marketing approval (conditional on completion of additional trials or risk management activity). Trials conducted as Phase IV trials may also be done by pharmaceutical companies for marketing purposes.

Source: IDC, 2004

Software Applications for Clinical Trials

It is estimated that cutting development time in half would lower the average cost of developing a drug from $802 million to $568 million.

Software applications generally address electronic data capture (EDC), acceleration of the clinical trial management process, and preparation of data for electronic FDA submission. Time to market is critical to drug development companies, as each additional day spent in development translates to significant revenue and competitive advantage lost. It is estimated that cutting development time in half would lower the average cost of developing a drug from $802 million to $568 million (DeMasi; *Pharmacoeconomics,* 2002, Vol. 20, Supp. 3, p. 1–10). The financial benefit of this acceleration has led pharma companies to explore EDC and electronic trial management technologies.

The codification of the Federal Food, Drug, and Cosmetic Act, the statute that empowers the FDA to regulate drug development, manufacturing, and marketing, and other U.S. laws enforced by the FDA can be found in Title 21 of the Code of Federal Regulations (CFR). When drug development data is generated, stored, retrieved, or transmitted electronically, the regulation at 21 CFR Part 11 (21 CFR 11) is applicable (in addition to other appropriate regulations). 21 CFR 11 is an evolving standard, and the FDA is continually altering and adding guidance on its implementation.

21 CFR 11 affects drug development by:

- Requiring clinical trial software developers to produce 21 CFR 11–compliant tools
- Requiring clinical trial software users to certify the 21 CFR 11 compliance of installation sites
- Placing additional certification requirements on trial sites willing to use EDC tools
- Requiring compliance of electronic tools that are used during the manufacturing of drugs in addition to compliance with current good manufacturing processes (cGMP)
- Adding barriers to the use of EDC tools in addition to those required by current good clinical practice (cGCP) regulations

Compliance with cGMP is critical for companies manufacturing drugs for sale and subjects them to submissions of manufacturing plans and details to the FDA, as well as mandatory plant inspections. Compliance is often assisted by software that automates supply chain management (SCM) and compliance of suppliers higher up the supply chain, as they all must comply with cGMP when materials that touch the finished drug product are involved. This is a growing area for software providers, both those regulated by the FDA and those regulated by ICH guidelines.

HIPAA also complicates the regulatory environment for clinical trial applications:

- It adds an authorization step that is similar but still distinct from informed consent. Patients must issue a "waiver" granting access to their "protected health information" (PHI) by investigators and sponsors and requiring investigators and sponsors to protect this data to the specifications of the law.

- It requires multiyear planning, including contingencies to list all parties who will need to view or analyze the trial data being collected. If parties are left out, additional waivers must be obtained.
- The patient's right to revoke authorization may in certain circumstances conflict with the FDA's desire to see and evaluate trial dropout patient data.
- Patient access to data, a key tenet of HIPAA, may conflict with protocols for blinded, placebo-controlled trials.
- HIPAA adds another layer of complexity in training and in monitoring and tracking compliance at investigator sites.
- Additional implications of HIPAA are discussed within the affected segment descriptions.

In summary, the environment for clinical software implementation is complex but resides within an enormous market with robust financial incentives to increase the efficiency of drug development and testing. Strong regulatory obstacles create obstacles to implementation of potential solutions. Opportunities for international harmonization exist, but multiple, inconsistent standards present additional barriers.

Business Practices and Segment Definitions

In further discussing the clinical trial environment, the potential solution providers, and the barriers to accelerating clinical studies, we must adequately define certain concepts.

- Clinical trial development, planning, and trial initiation:
  - Protocol design and execution
  - Institutional review board (IRB) review and approval
- Clinical trial management systems (CTMS):
  - Patient recruitment and study subject enrollment
  - Investigator relationship management (IRM)
  - EDC:
    - Electronic case report forms (eCRFs)
    - Patient diaries
  - Study monitoring and reporting
  - Clinical trial supply management
  - Cost tracking
  - Document management

- Adverse event reporting (AER)

- Study completion and regulatory filing:
  - Data analysis and reporting
  - Regulatory submission assembly
  - Communication and review

Due to the interrelated nature of the drug development process, many vendors have products that deliver integrated solutions that span more than one of the market segments listed above. They are described in greater detail below. For each segment, the competitive challenges are discussed, and two to three key vendors in the space are named and presented.

Clinical Trial Development, Planning, and Trial Initiation

Protocol Design and Execution

Clinical study protocols must comply with regulatory requirements for the geographic regions in which the company has determined it plans to seek approval. Although harmonization is making these requirements increasingly similar, each country still has administrative and clinical requirements outside the harmonized application. In the United States, the FDA's published guidance documents, in addition to meetings and conversations with the FDA, guide the development of study protocols by companies that are designed to prove the characteristics of the compound in question that the company proposed to market. A great deal of initial thought and planning is invested in development of the study's protocol, as design mistakes can lead to costly and time-consuming repeat or unsuccessful trials. Once the strategy and details of the trial are formulated by investigators, they are captured in a structured study protocol that includes the following:

- General and background information, including literature references
- Trial purpose and objectives
- Trial design description (methodology, randomization, patient treatment protocol) with schematic diagrams
- Protocols for handling subjects (inclusion/exclusion criteria, sample size)
- Selection of outcome measure(s), including data collection, data analysis, and statistical design and analysis
- Additional sections such as quality control, ethics, financing, insurance, publication expectations, and a statement of compliance with good clinical practice

An investigator's brochure (IB) is also required to accompany the protocol when submitted for review and approval prior to trial initiation. This document contains additional background material about the drug of interest, its manufacture and testing,

and any experiences that might be of value to the investigator in performing the trial. In addition, an informed consent (IC) form is developed that explains in simple terms the benefits and risks associated with participation in the trial to potential subjects. A signed IC is a prerequisite to the inclusion of a subject in a trial.

Software that is used to conduct protocol design can be relatively simple, as documentation requirements can be met using traditional word processing applications. However, the clinical phase of the study and the scope of the protocol often make the ability to collaborate across organizations or with outside groups desirable. Specialized software can better handle changes in a compliant manner when amendments to protocols are considered and can ease the writing of protocols for subsequent trials of the same or related compounds. Some applications have additional trial design validation functions of varying utility.

Companies that offer protocol design applications are typically small and/or are associated with academic institutions, but commercial vendors exist. Vendors of applications that assist sponsors in constructing study protocols are discussed in the following sections.

Academic Vendors

- API's BRAAN (**www.apibraan.com**) application, which was originally developed at the Baylor College of Medicine, is considered an industry leader in both protocol design and IRB management. BRAAN's functionality includes protocol authoring for both animal and human trials, versioning of protocol documents, and handling of attachments such as related grant applications. BRAAN's client base includes an impressive list of academic medical centers, and API uses a partner firm to provide strong implement assistance and support for the application.

- Open-source resources for protocol design include the National Cancer Institute's Cancer Therapy Evaluation Program (**ctep.info.nih.gov/guidelines/index.html**) online resources and the National Institute of Health (NIH) Clinical Center's ProtoType protocol writing tool.

Commercial Vendors

- **DataLabs.** DataLabs' products are built using Microsoft technology (Office, Visio, .NET), and the company's clinical study design tool, DataLabsXC Designer, uses Microsoft's Visio to enable drag-and-drop modeling of clinical protocol design attributes such as visit schedules, data types, and edit checks. The Designer module is part of the DataLabsXC product suite (**www.datalabs.com**).

- **Fast Track Systems.** Fast Track Systems' products include Trial Space Protocol Designer, which is part of a larger product suite used by Eli Lilly (**www.fast-track.com**).

Once a study protocol is assembled, submitted to the FDA, and approved, the trial begins. At this point, the protocol is advanced to the clinical investigators who will execute it under contracts with specific milestones and requirements.

Institutional Review Boards

IRBs consist of both clinical research professionals and nonclinical participants who have agreed to review and monitor biomedical research involving human subjects on behalf of an institution. Clinical investigators are responsible for submitting protocols to their IRB for approval, and some IRBs may require modifications prior to execution, further complicating the handling of protocol versions. The FDA provides guidelines on IRB composition that can be found at 45 CFR 46 (**ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm**). Additional guidance is provided by the National Bioethics Advisory Commission (**www.georgetown.edu/research/nrcbl/nbac**). IRB participants do not review and monitor their own research, only that of colleagues at their institutions. The goal of the IRB oversight is to ensure protection of the rights and welfare of human research subjects.

IRBs have traditionally been problematic for trial sponsors who rely on the IRB to promptly approve protocols and protocol amendments. Although investigators are compensated for participation in clinical research, IRB members are not compensated for their work. This creates a conflict of interest for the IRB-member doctors/investigators who want to focus on their own research and patients and do not place as high a priority as sponsors would like on their IRB responsibilities. To prevent this conflict from jeopardizing the safety of human research subjects, the FDA has created specific regulations to govern IRB members, their responsibilities, and their relationships to the studies they review. These regulations are followed by both IRBs affiliated with academic institutions that conduct research and private IRBs that also serve sponsors in the industry.

IRBs evaluate clinical trial protocols and related materials for compliance with GCP and ethical considerations and approve, require modifications to, or disapprove proposed clinical research protocols and other trial documents, along with monitoring studies. Their overall goal is to ensure continued protection of the rights and welfare of human research subjects.

Mounting pressure for rapid clinical trial enrollment and shorter trials have increased safety concerns and placed IRBs under increased scrutiny. In 1998, the Office of the Inspector General (at the HHS) issued a report on the state of IRBs, noting obstacles to effective IRB function. Among the barriers noted were too many protocols needing review, inadequate expertise on IRBs, and the inability to self-monitor IRB effectiveness. IT tools have the potential to help IRBs become more successful at these activities.

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Helpful IRB review and approval tools include systems for handling and distributing documents, conducting collaborative review, and managing version control. However, additional useful functionalities are generally included in IRB-targeted products. They encompass the above functionality, but may also enable interfacing with email, electronic submission, or other applications. IRB applications are typically purchased by institutions for support and facilitation of their IRBs. The leading academic IRB support application in the United States is API's BRAAN.

Table 2 describes a number of IRB support applications.

TABLE 2

Point Solution Providers of IRB Management Tools

	Product	Description
API	BRAAN	Developed at Baylor College of Medicine; award-winning application with multiple implementation methods and third-party support; protocol design, implementation, and IRB support, including generation of meeting agendas and minutes (**www.apibraan.com**)
Topaz Technologies	Assuring	DMS with integration, record retention, electronic submission, training, and email integration tools (**www.topaztracks.com/products/irb.html**)
Georgia Tech Research Institute	IRBWISE	Web-based DMS (**www.irbwise.com**)
ProIRB Plus Inc.	ProIRB	Microsoft Access-based tool with DMS and broader functionality for meeting agendas and actions, ongoing document management, adverse event recording, and auditing (**www.proirb.com**)
Dartmouth College/Children's Hospital of Philadelphia	IRBNet	Open source database application that supports communication and information exchange between IRB members, sponsors, and investigators (**www.irbnet.org**)

Source: IDC, 2004

Clinical Trial Management Systems

CTMS help manage all aspects of clinical study planning, preparation, performance, and reporting. CTMS encompass trial data such as documentation (e.g., protocols and case report forms [CRFs]), patient recruitment and enrollment, IRM, monitoring, reporting, and cost tracking. CTMS products might deliver a full spectrum of integrated solutions, typically including the following functional areas:

- Investigator recruitment and relationship management
- Investigator site identification and recruitment
- Investigator site management (grant payment management, financial disclosure, monitoring enrollment relative to plan)
- IRB management
- Protocol and IB document preparation
- Case report form development
- CRF planning and distribution (whether electronic or paper)
- Clinical supply management, including supply tracking, storage, and shipment
- Clinical data processing, including data acquisition, AER, and data storage

- Medical monitoring (CRF and other quality auditing) and reporting
- Adverse event tracking and documentation
- Data storage and management

Some products may offer a subset rather than all these modules, but by definition, CTMS deliver solutions spanning the clinical trial planning and performance timeline. Systems that manage this spectrum of information must be compliant with 21 CFR 11 to ensure that protocols, investigator brochures, CRFs, CTM information, and clinical data remains attributable, traceable, and controlled. This assurance is provided in CTMS by underlying document management systems (DMSs) that themselves are Part 11 compliant, but they must be coupled with adequate training and documentation of the entire system's configuration and stability.

Integrated CTMS Providers

IDC has defined an integrated CTMS provider as a vendor that provides functionality in four or more of the previously defined functional areas. Industry-leading full-spectrum solutions include:

- **Siebel Clinical.** This portal architecture helps track, profile, and manage investigator sites and personnel and manage clinical sites through calendars, trip report templates, payment management tools, and study manager tools such as CRF templates to help manage data collection and study report templates.
- **Oracle.** Increasingly, Oracle is expanding beyond EDC to develop (or acquire) a suite of point solutions that may be integrated into a full CTMS. As many of these systems are best-of-breed solutions in their own right, this developing suite holds promise as an integrated CTMS. Current functionality resides in the EDC, CRFs, AER, and study monitoring and reporting areas. Additional functionality is available via partnerships and integration.
- **International Management Package for Administration of Clinical Trials (IMPACT).** Formerly available through Fraser-Williams and now offered by Perceptive Informatics, a division of Contract Research Organization (CRO) Parexel, IMPACT supports planning (integrates with Microsoft Project), documentation, clinical payments, and deliverables (it provides an investigator portal to manage clinical site recruitment, enrollment, and document preparation). IMPACT is compatible with interactive voice response (IVR) systems, imaging review and storage applications, and Initiator and Investigator packages. There are currently 14,000 users globally.
- **ClinSource.** TrialXS has four modules that address trial management, electronic clinical data capture, CRF design and versioning, reporting, statistical analysis, and data verification.

Other, smaller CTMS vendors include ArisGlobals' globalTRIALS, Winchester Business Systems (WBS), Sierra Scientific Software's CRIS system, and Dendrite Clinical. Phase Forward may also be technically considered a CTMS vendor, but it

lacks full functionality in a fourth area, despite functionality in several areas beyond its core EDC, CRF, and AER applications.

Patient Recruitment and Study Subject Enrollment

Recruitment is a bottleneck in the planning and performance of clinical studies. For drugs targeted at large patient populations (>1 million prescriptions per year), up to 5,000 patients are needed for the FDA to evaluate the clinical utility and safety of each NDA. For many orphan drugs and biologicals, the entire patient population may be as small as 5,000–6,000 patients, making it extremely difficult to locate enough subjects for clinical trials. Study subjects need to be recruited and enrolled in studies from early toxicology and pharmacology studies to full-scale, Phase III efficacy studies. Recruitment is further complicated for biologics, which require diseased patients in Phases I, II, and III, as the nature of the compounds make it impossible to conduct Phase I testing on healthy volunteers. Recruitment difficulties that lead to a small sample size often cause the FDA to impose conditional approvals with requirements for postmarketing (Phase IV) risk management studies.

Finding and enrolling study subjects delays 60% of trials by at least one month and 13% of trials by over six months (Sinackevich, Nick, et al.; "Speeding the Critical Path," *Applied Clinical Trials,* January 2004). Study protocols require subjects with specific conditions and complications and restrict studies from enrolling many of the potential subjects who volunteer. This limits the available patient population for studies and makes recruitment an ongoing challenge.

Subject recruitment typically occurs via physician referral, advertising campaigns, direct mailings, and internet registration. Additionally, marketing and working with patient organizations (e.g., the National Cancer Institute) during preclinical phases to identify populations has helped recruitment for trials of orphan drug candidates and biologicals.

All of these methods have been found wanting by trial sponsors, and new ways of identifying potential study subjects are being explored. Physician referrals are becoming more limited, as HIPAA privacy regulations now limit referrals by requiring waivers before patient data can be presented to investigators. As a partial solution, sponsors have globalized trials to access treatment-naïve patients, who tend to be more readily available outside the United States (Anderson, Diana; "The Patient Recruitment Market," *Applied Clinical Trials,* November 2003).

The Internet has provided an avenue to reach more potential study subjects, and many companies are using this tool to find and register people who would be interested in clinical studies. The general business model is to entice potential patients to "register" with the Web site, and the site generates revenue by offering advertising directly to the drug company sponsors, who also pay to access the registered individuals. The market for Internet recruitment is expected to grow with the increasing consumer awareness of healthcare system processes.

Leading Internet patient recruitment vendors include:

- Acurian has 6 million individuals registered, over 40,000 participating investigators, and over 100 protocol recruitments completed. Acurian allows

registration of patient profiles for future protocols as well as enrollment in those protocols currently recruiting.

- ClinicalTrials.com (parent company is Pharmaceutical Research Plus Inc.) claims to have completed recruitment on about 220 trials and have 1.7 million individuals registered.

- Additional companies include AmericasDoctor.com, Veritas Medicine (**www.veritasmedicine.com**), Current Controlled Trials (**www.controlled-trials.com**), EmergingMed.com (**www.emergingmed.com**), Centerwatch (**www.centerwatch.com**), and NIH's ClinicalTrials.gov (**www.clinicaltrials.gov**). Individuals can browse and search available clinical studies at the NIH Clinical Center's Web site (**www.cc.nih.gov**).

Once the subject has been identified by recruitment efforts, the process of qualification and enrollment begins. Enrollment includes obtaining authorization for review of PHI to qualify individuals for the study, conducting the eligibility review, informing the participant of the risks and benefits of the research, and obtaining written, informed consent from participants. This task is repeated in multiple clinical trial sites across the nation or around the globe.

The eligibility review consists of screening potential study candidates for suitability based on the inclusion and exclusion criteria of the clinical study. It is critical to the success of the study, as well as for compliance reasons, that record-keeping and callback information is stored reliably, and these tracking activities are a good match for enrollment software products.

Subject study enrollment software is generally purchased as part of recruitment services, or as part of a larger, integrated application designed for EDC. Phase Forward offers recruitment and enrollment services over the Internet via a partnership with Veritas Medicine. Novartis Pharmaceuticals offers online recruitment for its clinical trials via a partnership with eTrials (**http://etrials.novartis.com**), another vendor with strong recruitment and enrollment functionality. Key features of these applications include online prescreening, automatic scheduling of screening appointments, and reminders for screening visits. All of these features help to increase the enrollment rate and assist with early compliance.

Investigator Relationship Management

IRM tools include software that facilitates relationships among investigators, subjects, CROs (if applicable), and trial sponsors. Good communication facilitates long-term relationships between sponsors/CROs and investigators who have practical experience conducting compliant clinical studies. One-third of first-time clinical investigators never undertake a second clinical trial, translating to significant losses from investments in training and experience. Many of these one-time investigators cite communication as the reason for their dissatisfaction, giving sponsors a strong incentive to remedy these problems ("Using Customer Relationship Management Strategies," *Applied Clinical Trials,* April 2003).

Without good communication, relationships among clinical trial sponsors, investigators, and study subjects become transient and stressful, resulting in delays,

inefficiencies, and elevated costs. IRM tools have been developed to assist in forming relationships and maintaining communication during trials. It is clear that the regulatory requirements, the large number of participants, and the complex spectrum of activities required during the preparation for and performance of a clinical trial make the IRM space an attractive market for automated collaboration tools. However, the tools must be flexible enough to manage the uniqueness of clinical trial needs.

In addition to communication and collaboration tools, full IRM functionality includes investigator credentialing, master agreement and contract templates, CRF review and training, investigator/clinical manager training, grant management/payment tracking, and reporting. IRM systems often offer features that assist maintenance of both cGCP-compliant processes and HIPAA-compliant access protections. HIPAA compliance is required because IRM systems contain identifiable patient medical data. Systems must also be capable of providing compliance reports to auditors of HIPAA and cGCP regulatory compliance. IRB support functionality can also be a component (see the IRB Review and Approval section for more information). Web-based functionality and portal capabilities also help to pull together geographically and technologically diverse participants.

IRM solutions as described previously have many functions in common with traditional customer relationship management (CRM) tools, and successful IRM strategies bring aspects of a "customer" relationship into dealings with the investigators, IRBs, clinical research associates (CRAs), study subjects, CROs, suppliers, and other parties involved in trials. The market for CRM-like workflow solutions for clinical trials is still in its infancy, but Siebel Clinical is arguably the market leader, delivering a portal-based, full-spectrum, integrated solution. IBM offers a best-in-class solution based on Siebel's system but augmented by IBM's collaboration and distance learning tools (Lotus), reporting tools, and Cisco's Clinical Contact Center (for connectivity and IP telephony), all linked via IBM's portal technology.

The eResearch Community product from eResearchTechnology is similarly centered around a portal providing visualization and educational tools as well as chat room functions and access to personalized content related to investigator activities and training, product status, or whatever else is necessary to deliver to the clinical investigator or study site.

Winchester Business Systems and the Cmed Group also offer broad-spectrum IRM solutions, leaving smaller firms to address particular bottlenecks in the process, such as Intrasphere's remote conferencing capability and ePharmaLearning's online collaboration, meeting, and training product.

Electronic Data Capture

EDC has been around for at least 15 years, in one form or another. In the clinical trial space, EDC is generally considered to include electronic documentation of data from patients and clinical investigators during a clinical trial. Early implementations were not widely accepted, in part because of the high costs to support a thick-client architecture in a client server environment. The need for IT expertise out in the field, significant training costs, and inflexible user interfaces hindered the adoption of earlier versions of EDC products. Version control and updating/adding CRF content also presented obstacles. Many of these issues are resolved by applications that are

hosted and delivered via the Internet. The Internet is an ideal venue for EDC and has begun to change user impressions of EDC, and the current generation of vendors and products is experiencing much stronger adoption. Most of the newer products use Internet and Web interfaces that run on thin clients and are delivered by vendors who have a sophisticated understanding of the requirements.

The concept of putting CRFs on the Internet is a powerful addition to the EDC business proposition. By avoiding some of the preparation and printing costs of CRFs and effectively designing (and perhaps reusing) electronic forms, EDC can lower data acquisition costs. Advantages of collecting clinical information electronically (either via electronic patient diaries [EPDs], directly from instrumentation, or even from faxed or scanned source documentation) can also include more effective and more rapid data checking (mitigating the need for manual, double data entry), access control and data security, audit trails, and a single access point to the clinical information. Additional cost savings come from reduction of travel by site monitors, who can analyze electronic data remotely and schedule visits accordingly. Despite these obvious advantages, a majority of clinical trials are still completed using an entirely paper format.

Estimates of EDC use vary. Current use of EDC in Phase I–III clinical trials by pharma, biotech companies, and CROs is estimated at 24%, a substantial increase from 12% in 2000 (Bleicher, Paul; "Clinical Trial Technology: At the Inflection Point," *Biosilico,* November 2003, Vol. 1, No. 5, p. 164). However, this number is slightly misleading. In an IDC study, only 10–12% of these companies claimed "widespread" use of EDC, while an additional 25–35% claimed "limited adoption" of the technology. An additional 10–15% claimed to be evaluating the technology, while a disturbing 40–50% claimed to have never used, never evaluated, or evaluated and decided against using EDC (IDC Leading Indicators, November 2003). We suspect that there is some confusion regarding what constitutes adoption, as neither of these sources differentiated between the different forms of EDC implementation and/or hybrid implementations.

Electronic trials can be either all electronic or in a hybrid format:

- **All-electronic trials.** A trial is considered all electronic when the CRA enters data directly into an electronic (usually Web-based) CRF at the site of the trial. The data is then immediately uploaded to a central server that generates real-time queries, dramatically shortening the time between when a visit is accomplished and when the sponsor receives corroborating data.

- **Hybrid trials.** Hybrid trials are sites that operate entirely on paper records and CRFs, and the trial book is composed by clinical data managers in paper format. Once the forms arrive at the sponsor or CRO, they are entered into an electronic system using a cumbersome double-data entry model, and queries are issued. Different variations on this occur, as the exact point where the paper trial converts to an electronic one varies among hybrid trial instances. Additional data entry models also exist in a hybrid model, using IVR or scanning to incorporate documentation.

EDC systems may be installed software or Web-based applications. However, Web-based, thin-client systems are rapidly gaining favor with sponsors and investigators. Web-based systems are independent of the client hardware and allow all sites to be instantaneously updated with software and/or protocol changes. Data and applications are stored centrally and accessed in secure Web-based transactions. This prevents the need to certify sites for regulatory compliance beyond basic Internet connectivity requirements. There is no need to ensure security of local data because there is none.

Oracle and Phase Forward are the two major providers of EDC systems and share 50–60% of the market for EDC solutions. Oracle Clinical and Phase Forward's product lines (ClinTrial, Clintrace, and InForm) are considered standards in the industry. Phase Forward's InForm and ClinTrial products offer parallel functionality for all-electronic and hybrid trials, respectively, giving clients an array of automation options. These leading EDC vendors and some additional second-tier vendors are discussed in Table 3. It should be noted that several of the second-tier vendors have histories of instability, including financial address, which often influences sponsor decisions when selecting EDC products.

TABLE 3

Leading EDC Vendors

Company	Phase	Description
Oracle	All	Oracle Clinical and Oracle RDC support EDC, adverse event tracking, regulatory reporting/audits, data validations, multiple languages; highly customizable, largest installed base (**www.oracle.com/industries/life_sciences**)
Phase Forward	All	Inform and ClinTrial systems offer Internet-based and installed capabilities, respectively; solutions in EDC for all forms of trials, CDM and clinical workflow management. 482 clients used Phase Forward tools to operate trials at 12,000 sites in 86 countries in 2003; specialty site certification model; ClinTrace provides AER (**www.phaseforward.com**)
DataTrak		ASP-delivered product with good coverage of CRF and data validation process and emphasis on system performance; beginning to offer installed systems (**www.datatraknet.com**)
Parexel/Perceptive Informatics	I	Subsidiary of Parexel International (CRO), also markets IMPACT CTMS system; initiator product provides EDC for Phase I trials; also provides IVR, imaging, and portal capability (**www.perceptive.com**)
Outcome (formerly Outcome Sciences)	III, IV	Strong services to support AER and patient diaries in late-phase trials and postmarketing approval (**www.outcome.com**)
etrials	I, II	QuickStudy product for Phase I and II products; HP handheld device partnership; rapid growth; strong internationally (**www.etrials.com**)
eResearchTechnology	III, IV	Late-phase cardiac trial expertise; portal functionality (**www.ert.com**)
DataLabs		Microsoft collaboration for EDC capability integrated with Office, Sharepoint Portal, and Visio applications (**www.datalabs.com**)
Nextrials	All	Prism application features strong integration with clinical systems, particularly lab information; all XML/CDISC compatible; supply and AER functionality strong (**www.nextrials.com**)

Source: *Bio-IT World Buyer's Guide,* 2003

Case Report Forms

CRFs are sponsor-defined forms (paper or electronic) on which patient data pertaining to the particular study is recorded by clinical staff at the sponsor site. Electronic generation of CRFs is the main component in any EDC system. Once data is entered into CRFs, it is compiled in a master clinical database (MCDB) for each trial. From this database, analysis is conducted to determine the results of the trial, which is then submitted to the FDA in support of an NDA. Although analysis is conducted on the MCDB, the FDA investigators may, under certain circumstances, need to drill down to the actual CRF to validate data, and sponsors must maintain the "source data," consisting of original CRFs and medical records data. It is the need to confirm that CRFs represent the true source data that is at the crux of the quality assurance issues regarding the collection and storage of clinical data, regardless of whether that is accomplished with paper or electronically.

Several scenarios exist for CRF automation, representing various levels of automation in the models described in the Electronic Data Capture section. CRFs, whether on paper or by hand, must be signed by investigators, and an audit trail documenting all edits/changes must exist. Most vendors providing eCRF solutions offer 21 CFR 11–compliant solutions using electronic signatures.

As with all aspects of clinical trials, handling of CRFs varies according to the regulatory requirements of the country in which the trial is performed. Global trials can have multiple formats for different countries, with participants who vary in their experience with particular technologies. Vendors and sponsors must be able to handle a variety of arrangements, although electronic systems are rapidly gaining ground. Obviously, the large amount of paper, the nature of the form-driven data collection, and the archiving requirements cry out for electronic handling, and the industry is finally heeding this call.

The advent of 21 CFR 11 has helped make electronic CRFs a reality, with guidelines for electronic signatures and data handling. The market for computer-based CRF handling applications, as well as laptop and PDR-based applications, has grown significantly over the past two years and will continue to grow rapidly. CROs usually provide electronic CRF handling services as part of their product offerings. In about 25% of cases, the software and databases are proprietary applications developed in-house by the CRO, but in the majority of offerings, a third-party vendor is partnering with the CRO to provide the underlying infrastructure of software and devices.

The leading software vendors in this subsegment are Oracle Clinical and Phase Forward, which are discussed in the Electronic Data Capture section and provide CRF handling as part of more comprehensive EDC products. Additionally, many smaller vendors exist to support or automate some aspect of CRF handling and data validation at the sponsor sites. These smaller vendors often create value through a specialized clinical foci and provide customized CRF applications and data entry forms already tailored to a particular disease.

Other strong vendors include eTrials, DataTrack, DataLabs, CRF (formerly CRF Box), invivodata, and Outcome (formerly Outcome Sciences Inc.). Also, Microsoft's Visio product is incorporated in the offering from DataLabs.

Electronic Patient Diaries

EPDs are used in place of paper diaries in both clinical trials and postmarketing studies for subjects to self-report data (called patient reported outcomes or PROs). Electronic diaries provide dramatic, documented advantages over paper that include improved subject compliance and accuracy of data reporting and analysis. This improvement in compliance was demonstrated recently in a study sponsored by the National Cancer Institute and recognized by the FDA.

It is estimated that diaries are currently used in more than 25% of clinical trials ("Patient, Record Thyself," *Bio-IT World,* July 2003), but only 5–10% of the diaries used in studies are electronic (IDC Leading Indicators, December 2003). The four major types of EPDs are differentiated by the hardware used: telephone/mobile phones and IVR systems, PDAs and other handheld devices, tablet/laptop PCs, or desktop computers. The market may be further segmented by the nature of the companies (i.e., whether they are hardware or software focused and whether they provide additional components of an end-to-end clinical development solution or specialize in EPDs).

The primary factor in drug development users' buying decision for EPDs appears to be the format of the hardware and software and its appropriateness to a particular protocol. Relationships between EPD providers and the sponsors of clinical trials must be forged during the protocol development phases to be successful, as information to be captured and the patient demographics should be matched to the technological solution. EPDs can be used in conjunction with other EDC products as part of a sponsor's clinical trial strategy.

Three leading EPD vendors are:

- **ClinPhone.** ClinPhone IVR is widely used by pharma companies for data reporting, including patient reported outcomes. Other uses include supply management, project management, randomization, and coding. Web-based reporting is also available (**www.clinphone.com**). ClinPhone has a relationship with Phase Forward that allows the information gathered in its diaries to be incorporated into the MCDB for the Phase Forward application.

- **CRF.** (formerly CRF Box) CRF's TrialMax product is widely used data collection software that uses PDAs and cellular text messaging as inputs (**www.crfhealth.com**).

- **invivodata.** The invivosystem Palm-based EPD allows patients to document experiences in Phases II, III, and IV trials. The company has specialized expertise in gastroenterology, pain management, and respiratory trials (**www.invivodata.com**).

Study Monitoring and Reporting

CRF data is derived from source data, which is stored in the subject's personal medical record and includes laboratory test results, clinical observations, provider notes, dictation, and other forms of clinical documentation. Over the duration of the trial, CRAs from the sponsoring organization (or members of the sponsor's Quality Assurance unit) transfer source data to CRFs, validate this data, and document revisions. Documentation of revisions requires a formal audit trail. CRAs also review the clinical site's patient accrual and enrollment data to ensure that subjects are enrolled in appropriate numbers and meet the inclusion/exclusion criteria specified by the study protocol. At every point in the trial, CRAs work to ensure document regulatory compliance. Audit reports are also prepared by CRAs to document compliance for sponsors.

Audit reports determine whether the investigator is asked to participate in additional studies, requires additional training, and receives payments and incentives. The degree of risk that study subjects are exposed to must be consistent with the monitoring requirements — a more risky clinical study means more audits and more rigorous investigations and reports. Based on the amount of time invested in these audit visits and the subsequent report generation and the central role the reports play in assuring the FDA that the data resulting from the trials is representative of the source data, tools that can assist the CRA perform these auditing functions and ensure the compliance of the clinical sites are helpful. Although some small point vendors exist, these tools are typically part of other documentation packages and/or of broader CTMS.

During the course of a trial, researchers may also wish to perform meta-analysis to confirm progress or sample results pending a potential protocol change. For this purpose, extracts are generally taken from the MCDB, and the leading EDC applications facilitate this functionality. The extracts are analyzed at the sponsor site by the sponsor's analysts if data must be unblinded, but can be analyzed at a clinical site or by the trial's data monitor in the case of a single-blind or open trial. The most commonly used application for this analysis is SAS.

Clinical Trial Supply Management

Clinical trial supplies (CTSs) represent the first manufactured lots of drug product that will be administered to man. They must be made in compliance with cGMP, and they will be administered in compliance with cGCP. The clinical trial materials (which may also include inert placebo products) are typically provided in kits with labeling appropriate for the study (in a double-blind study, the investigators and study participants will not know the composition of the drug to be administered, although the clinical protocol will ensure dosing is appropriate), instructions for use, and additional documentation or storage instructions. Parameters such as storage temperatures and expiry dating are relevant, and the clinical trial materials must not be exposed to conditions outside the validated storage envelope for the product or the clinical study could be jeopardized. These kits represent enormous investments in time and money, and the implications of the clinical trials for further development are huge. Thus, it is imperative to track the whereabouts, control the condition of CTSs, and ensure adequate supplies reach the clinical study sites to meet the protocol requirements.

SCM software has typically been utilized to provide CTS management functionality in the pharmaceutical industry. Clinical trial materials produced under cGMP compliance have resource management and tracking requirements similar to those of marketed pharmaceuticals. As in other industries, cost savings have been estimated to justify purchasing and implementing significant enterprise applications. Accenture estimated that excellence in SCM systems could save about 40–50 days of drug development time ("Next-Generation Clinical Supply Chain Management Systems," *Pharmaceutical Engineering,* September/October 2002). Another way of looking at return on investment (ROI) is to assume revenue of $1 million per day for a nonblockbuster marketed product. Getting to market 50 days sooner, and thus having 50 days of additional market exclusivity, is a significant driver to the implementation of effective SCM systems.

CTS management functionality in the life science industry has been delivered by enterprise solution providers such as Rockwell Automation (Propack Data suite), Honeywell's POMS application, Manugistics, SAP, and others. With providers of ancillary functionalities spreading into this space (see ClinPhone's recent expansion to include a CTS management module), there will be many options for sponsors to consider, depending on the complexity of the manufacturing and distribution process, as well as how integrated a view of business processes they seek.

In this environment, full-fledged SCM and ERM vendors may find competition is not from traditional sources, but from focused providers of specialized packages that integrate easily and less expensively into their current clinical trial management solutions.

Cost Tracking

Cost tracking functionality is often delivered as part of an integrated CTMS solution or within the context of an IRM and/or CTS management product. Typical functions include study center budgeting and tracking of expenses such as:

- Payments to investigators
- Enrollment bonuses
- Patient payments
- CRA payments
- Site visit expenses

When included as part of a broader solution, cost tracking becomes an element in the total view of the trial progress and another means to make better trial management decisions. Ideally, these cost tracking functions would be integrated with the SCM functions described in the previous section, but many smaller biotechs or CROs may find that the cost tracking (as well as other) tools already available in integrated CTMS solutions are adequate and financially more reasonable to implement than buying in to an enterprise SCM and accounting solution.

Document Management

The definition of DMS within the life sciences segment varies widely among vendors. Typical functions include document control, organization and indexing of documents, collaboration, publishing, scanning, security, ensuring regulatory compliance, archiving, and data and text mining. Preclinical and in vitro study solutions may include electronic laboratory notebook and laboratory information management system (LIMS) functionality or connectivity to third-party systems. Vendors must offer proven 21 CFR 11 compliance and Web-based or distributed solutions to compete.

DMS vendors include:

- **Documentum.** Documentum (**www.documentum.com**) is clearly the market leader in providing DMS solutions to life science, as well as many other vertical industries. The recent purchase of Documentum by EMC provides a strong signal that integrated content and document management solutions on stable storage platforms enabling secure, appropriate, enterprisewide access on demand is a vision that should soon be available to accelerate the knowledge sharing and information management that could drive down the time and expense of managing information.

- **Liquent.** Liquent's InSight Foundation is the closest competitor to Documentum (**www.liquent.com/insight_foundation_overview.asp**) and provides a DMS structured around industry best practices and the CTD and eCTD requirements.

- **First Consulting Group.** First Consulting Group (**www.fcg.com**) provides a preconfigured solution called FirstDocs that is built on top of the Documentum products.

- **Qumas.** Qumas provides a "platform neutral" document compliance package that can run on top of either Documentum or a relational database system like Oracle (**www.qumas.com**).

In addition to these market leaders, there are numerous point solutions, such as Ecora's Configuration Auditor (**www.ecora.com**), that help ensure that enterprise systems are controlled by querying networks and generate maps of the network architecture and settings to laboratory notebooks useful in capturing test and study data and images (such as Nugenesis).

Adverse Event Reporting

AER is required both during the clinical trial stage and after drug approval. In the United States, adverse drug experience reporting is required by the FDA under 21 CFR, and events must be coded using the MedDRA vocabulary. AER includes:

- **15-Day reports of serious, unlabelled events and serious, labeled events.** These reports must be submitted within 15 days of the sponsor receiving information about the event on the FDA-approved 3500A Medwatch form. They must be submitted to the FDA at all points in clinical development and postmarketing. Life-threatening adverse events must be reported even more quickly.

- **Periodic safety update reports (PSURs).** These reports are required by the FDA and are expected to become a component of the ICH's guideline for AER. PSURs must be submitted to the FDA at all points in clinical development and postmarketing.

- **Compliance with international standards.** Globally, AER standards vary, and applicants/manufacturers must comply with all of the international standards to submit reports. International reporting standards include CIOMS-I, CIOMS-II, ICH E2B (EU), ICH E2C-compliant PSUR line listing, the FDA-approved 3500A MedWatch, the French CERFA, the German BfArM, and MCA Clinical and Spontaneous reports.

In all of these cases, the applicant or manufacturer has reporting responsibility.

To complete the different adverse event reports in the time frames required by regulatory organizations, applicants/manufacturers must implement a tracking, investigative, and report generation capability to gather the required information and generate AERs. In many cases, this is a manual system. However, automated applications are becoming widely used and are available as standalone systems or as add-ons to integrated CTMS, document management, and other point solutions.

The two leading AER applications are:

- **Oracle Clinical.** Oracle Clinical's AER module is the leading application. Adobe PDF-format Medwatch forms can be generated from within the application for direct submission to the FDA.

- **Phase Forward.** Phase Forward's Clintrace includes predefined reports to comply with international standards and also includes workflow tools such as tracking and deadline alerts to assist users in creating and submitting reports. Clintrace automatically generates FDA- and E2B-format adverse event reports and PSURs and enables MedDRA coding. Clintrace can be used standalone or alongside Phase Forward's ClinTrial and InForm products.

Second-tier AER vendors include:

- **NetRegulus.** NetRegulus' AER function includes management of events with patient or user implications. Potent search-and-selection tools are available to quickly find adverse event issues and create new investigations. Users can attach digital records, assign tasks, and generate letters from within the application (**www.netregulus.com**).

- **Aris Global.** ArisG application enables the real-time collection, coding, reporting and analysis of pre-and postmarketing adverse events. ArisG can be deployed as a client-server or Web-based solution and supports some international reporting standards (**www.arisglobal.com**).

Study Completion and Regulatory Filing

Data Analysis And Reporting

Analysis of data obtained during clinical trials is complex and must be done using tools and methods carefully monitored by the FDA. For the most part, the analysis and the methods that will be used are determined long before the trial begins, as the sponsor plans for data collection using the required methods to meet the objective of the trial. Most trials incorporate some form of meta-analysis during the trial, using preliminary data to confirm the trial design and check on results while changes to the protocol can still be made. In some cases, if the trial design is flawed or results are not as expected, "data dredging" is done, which involves remanipulating data after the conclusion of the trial. This process is frowned on by the FDA. The FDA also insists on receiving raw data from sponsors that FDA statisticians use to perform their own analysis.

In the market for tools for FDA-compliant analysis of trial data, SAS holds a commanding position that is largely unchallenged (SAS files have been the accepted standard at FDA since 1999). In the expected guidances on eCTD, the FDA will certainly reaffirm its desire to receive SAS Transport files along with the XML backbone files enabling data analysis and review. Further, SAS mining tools have recently been licensed by FDA for performing their own statistical analyses. Further reinforcing the dominance of SAS in this space is an ecosystem of small consulting firms that specifically provide SAS programming and analysis for clinical trials.

There are other potential solutions in this space, with a number of vendors providing complementary functionality to SAS. SyTech (**www.sytech.com**) and Wimmer Systems (**www.wimmersystems.com**) have implemented a 21 CFR 11–compliant solution to augment Excel datasets (which are otherwise unacceptable to FDA) with appropriate audit trails and other controls. The ARISg product of Aris Global provides real-time analysis and adverse event coding of clinical trial data, and the Aris E2B Gateway is a Web-based reporting tool enabling secure, encrypted transmission of such information.

Interestingly, the FDA has chosen products of the Insightful Corp. (formerly MathSoft) for monitoring clinical data and for analysis that complements traditional statistical software such as SAS. Clearly, with its enormous databases of clinical and toxicological data, the FDA is interested in innovative data mining and analysis capabilities. Coupled with mechanisms that report clinical data from trial sites or from a sponsor's regulatory groups, there are likely a number of avenues to provide useful additions to the brief roster of accepted solutions in this space.

Regulatory Submission Assembly

Marketing approval for drugs and biologicals in the United States requires successful completion, submission, and approval of an application to the FDA, constituting an NDA for drugs or a BLA for biologicals. The ICH has developed a CTD and an electronic version, the eCTD, that are now accepted by regulatory agencies in the three main drug consuming regions in the world: the United States, Japan, and Europe. This document harmonizes some of the requirements, but there are still country-specific variations in the review process and the clinical and administrative

requirements, although the format and order of the document are consistent. The assembly of regulatory submissions to meet country-specific regulatory requirements has traditionally been a manual, labor-intensive process in which information from a number of disparate locations and departments within an organization would need to be collected, integrated, and formatted to meet submission requirements.

In an attempt to increase efficiency and the likelihood of success, this process has been the target of many process modifications. As part of this process, the industry and the FDA increasingly have moved toward the use of relevant IT tools. The application of these tools is a priority for many pharmaceutical firms (of all sizes) and CROs contracted to perform this function for their clients.

Submission assembly tools include functionality that:

- Assists with regulated document assembly from controlled documents stored in a DMS organized in a manner that facilitated the assembly of the application
- Complies with the harmonized CTD as well as country-specific formatting and content requirements
- Complies with electronic format regulations when submitting electronic applications
- Stores submission data in a controlled environment, maintaining links to source data and other materials regulatory agencies could potentially request during the approval process

Liquent is a leading provider of content assembly and submission solutions for the life science industry (founded as Electronic Submission Publishing Systems [ESPS]) with its flagship product CoreDossier (**www.liquent.com**). Additionally, when EDC systems are used in data collection, vendors may include functionality that extracts and converts clinical and administrative data into formats appropriate for submission.

Communication and Review

Communication tools span all aspects of the clinical data acquisition process, from CRF planning and acceptance (as exemplified by Image Solutions' CRFTrack, which provides EDC of information directly into eCRFs for appropriate routing for QA and storage in EDMS for eventual incorporation into esubmissions) to submission and approval negotiations.

Regulatory submissions have traditionally been paper documents consisting of (for new drugs) hundreds of thousands of pages. Over the past decade, the FDA has developed the capability to accept and review submissions that contain documents in digital formats and has developed its Part 11 strategy to ensure electronic documentation is as secure as paper submissions. As the FDA's goals for digital submission have grown, the industry has struggled to provide appropriate software tools and documentation formats. Only recently has the FDA developed templates for the variety of regulatory documents that must be submitted for review.

Vendors have responded by releasing software designed to assist sponsors in collecting the necessary information and assembling it into a compliant regulatory document. These firms include a variety of partnerships and independent and allied ventures among CROs, consultancies, traditional software vendors, and drug development companies.

At the submission level, Liquent has leveraged its position in the submission assembly space by integrating it with document (and content) management and collaboration. Liquent's Clarity product facilitates collaboration by transforming content into XML for distribution across a company or between companies (or to the FDA). Additionally, all of the document management systems play critical roles when applicants are asked by the FDA for additional data during the approval process, as efficient access to existing data is crucial to a fast turn-around on these requests, in order to minimize delays.

Communications, both intra-FDA and between FDA and industry, require secure email communications. Outside the closed network of a corporate or governmental institution, commercial solutions such as the Secure Public Network marketed by Tumbleweed Communications (in use by the Center for Drug Evaluation and Research [CDER] at the FDA and pharmaceutical companies including Amgen) will be useful (**www.tumbleweed.com**).

Custom Solutions

In a study published in early 2003 (*Discovery Through Clinical Trials: IT Infrastructure and Needs Segmented by Workload,* IDC #3784, July 2003), IDC found that for clinical trials, over half of all application software is developed by in-house programmers or by outside contractors for specific use. This was the highest of any of the R&D segments covered in the study.

Although it is outside the scope of this document to do primary research on the motivations for relying on internally developed software, there are a general set of conditions that IDC believes contribute to the high degree of custom software. These include:

- **Variation.** There is a large amount of variation in the protocols and SOPs from company to company and from trial to trial within a company.
- **Dependence on paper-based systems.** When pharmas and CROs do go electronic in clinical trials, they often have a desire or need to make the electronic system identical to the preexisting paper-based system. This need to match the previous system and to integrate electronic tools with paper-based tools and processes lends itself to making the decision to develop custom solutions.
- **Cost savings.** Application software vendors that emphasize customizability, rather than configurability, tend to drive the customer base to the conclusion that it is just as cost-effective and more functionally complete to simply develop custom applications. When the cost of customizing a commercial product to make it fit the customer's requirements gets so high that it approaches or exceeds the cost of programming an application from scratch, customers will choose to develop a solution themselves.

CROs clearly drive a significant amount of innovation in this space. According to Kalorama Information, CROs made up over two-thirds of the market for outsourced clinical research in 2002, which was a nearly $14 billion business, and are expected to double by 2008. Smaller site maintenance organizations and other small entities involved in data handling are also expected to grow their revenue, if not market shares, through 2008.

FUTURE OUTLOOK

Insight

With over 80,000 clinical trials underway globally (Centerwatch) and over 30,000 participating clinical investigators, the opportunity for vendors to develop solutions to support accelerated clinical trial activities is significant. The Tufts CSDD has stated that up to 48% (CNS agents) of drug development cost is related to the time spent in this phase and that "cutting development time offers a potent tool for containing R&D expenditures" (Impact 2004). It is impossible to cut some of the time spent in drug development, but in some areas, it has been proven that a careful and innovative approach to implementing IT solutions has the potential to dramatically reduce costs. The six application areas that IDC feels have a high potential to add efficiency and reduce costs in the clinical trial segment include:

- Integrated CTMS
- Decision support systems
- EDC
- Interim and final data analysis
- Supply and cost tracking

In a recent column in the Association of Clinical Research Professionals' publication, *Monitor*, industry columnist Ronald Waife states that the CTMS space "remains the most confused, fragmented, yet critical component of the clinical research IT world."

Integrated Systems

The first area selected as a target for vendors is integrated CTMS. In the discussion above, several vendors are cited, and their solutions are promising, but when compared with the stated needs of end users and solutions available in other verticals, the area is clearly underserved. In a recent column in the Association of Clinical Research Professionals' publication, *Monitor*, industry columnist Ronald Waife states that the CTMS space "remains the most confused, fragmented, yet critical component of the clinical research IT world." He continues, "it is hard to find two applications in this space that cover the same set of users or needs" (*Clinical Research Technology,* 2003). IDC certainly agrees with this point of view.

An ideal system in this space would integrate EDC with project management for both sites and sponsors. Data visibility is a major component, as sponsors want high-level data about trials, but also requires the ability to drill down into detailed data for specific information on progress and events. True CRM functionality facilitates communication between investigators and other trial participants. An intrinsic hurdle for integrated solution vendors is the issue of multiple sponsors conducting trials at

the same site, while clinical professionals at sites struggle to avoid installing, learning, and using multiple applications. Web-based systems developed in the past 5 to 10 years have eased this problem, and Web services/XML technology has the potential to bring about a resolution. Still, it remains for a vendor to invest the time and expense necessary to provide a workable solution for this space that truly meets users' needs.

Decision Support

Decision support in the healthcare and clinical trial arena has always been a difficult proposition. It has been proven that efficiencies and, in the case of healthcare, improvements to outcomes can be created through the use of these systems, yet their effect on provider autonomy is difficult for the industry to manage. A similar quandary exists in the area of clinical trials. We know that systems to assist investigators in maintaining adherence to protocol and recording and managing clinical data can improve data quality while speeding the conclusion of trials and the subsequent analysis of data from trials. However, the tradition of clinical research creates obstacles to companies that want to automate the requirements of the drug approval process.

This is an area in which innovation is needed by vendors. Healthcare has approached this question in primarily a retrospective and stick-based approach. Provider report cards, the threat of malpractice, and declining reimbursement have driven adherence to guidelines and use of decision support tools such as Computerized Patient Order Entry and Electronic Health Record systems. In clinical trials, the approach needs to be real time and proactive, but usage can still be tied to reimbursement and incentives. Tools need to be developed that provide intelligent support in the area of protocol design, compliance with protocols in the field, EDC, and AER. Although there has been some exploration into this by companies, there is still significant room for innovation. The cost of clinical research has begun to drive this process, and again, there is a significant opportunity for vendors in this area.

Electronic Data Capture

Most major pharmaceutical companies in 2003 had some adoption initiative for EDC on the books, whether in the form of an actual vendor contract or a publicly announced program. However, an estimated 80–90% of clinical trials still remain paper based. Vendors like Phase Forward and Oracle have made important strides forward into mainstreaming the EDC process, but additional progress still needs to be made. Although the FDA has made some missteps guiding the implementation of 21 CFR 11, it has also made massive efforts to work, often one on one, with vendors and industry to develop the standards needed to remove stumbling blocks to implementing and adopting solutions.

Process changes must accompany EDC implementation. Accenture, in its 2001 report, High Performance Drug Discovery, recommends operational optimization, better management of information and knowledge, and utilization of technological advances as necessary to improve the hit rate for drug development. From the application side, many pharma firms have already committed to electronic clinical trial activities and have aligned their infrastructure across the enterprise, providing high-

bandwidth connectivity, scalable integration frameworks, and clinical portal servers to deliver applications covering previously discussed functionalities. A recent survey by *R&D Directions* (published in November 2000), reported that over two-thirds of pharmaceutical R&D executives see a need for internal efficiency improvements as a key factor driving the integration of electronic information tools into the drug development process.

Looking to the future, more than half of R&D executives see Internet-related technologies as fundamentally changing their R&D processes, and nearly two-thirds see a high level of urgency for new Internet technology. A majority believes this technology will result in shorter time to market and lower development costs for new drugs.

Overall, the drivers for continued adoption of electronic tools in clinical trials suggest strong growth for the future. However, the various barriers and the highly fragmented nature of the vendor landscape pose perils for vendors trying to establish a large-scale business within this market.

Interim and Final Data Analysis

The potential for EDC to make data feeds from clinical trials available to sponsors and their data analysts in real time, as the trial is progressing, has yet to be fully exploited. *In silico* trial technology and group sequential trial designs are beginning to get more attention, but their true potential will come only when these ideas are combined with EDC. Good trial design helps sponsors do the right trials first, and development costs go down when compounds are approved the first time the application is submitted to the FDA. Repeat and inconclusive trials clearly have a massive impact on drug development time and cost. Real-time data and analysis promises to allow sponsors to identify and abort or refine those trials that are headed for failure at an earlier point. It will allow them to find trials with flawed designs before months and possibly years are wasted. This value proposition is an opportunity for vendors who can provide integrated tools that work with both EDC and statistical toolsets to automate early data analysis and put structure into decisions that occur during the course of a trial.

Cost and Supply Tracking

The cost and supply tracking problem is endemic among clinical trials. Applying conventional SCM and financial management solutions to trials has traditionally been inconvenient and inefficient, due to the short time of most trials and the investment required to implement and use such complex systems. However, newer Web-based systems should allow more refined tracking of costs and supplies for trials. This will lead to hard benefits from being able to better control costs, as well as some soft benefits. For example, prompt and accurate investigator compensation is a major issue in increasing satisfaction with trial participation for investigators. By increasing investigator satisfaction, sponsors will be able to keep experienced investigators engaged for multiple trials, eventually improving trial performance while lowering training and recruitment costs.

Additional Insights

In addition to the areas identified above, several others remain that have no obvious solutions, such as subject recruitment. These obviously present opportunities, although not necessarily to IT vendors. However, it should be noted that along with all the areas identified, there is room for innovation along with investment in improving existing solutions.

ESSENTIAL GUIDANCE

Action

The question of how to answer the call to action created by the opportunities in the clinical trial management space is a difficult one. The following is clear:

- The business case and the regulatory environment are moving toward acknowledging the value of integrated enterprise solutions that bring modern business analytical tools into the distributed process of clinical trial planning, performance, and reporting.
- A successful vendor in this area will base its offerings on extensive research into processes and requirements and investment into evaluating customers' needs and adopting the functionality that meets them. A successful solution will be highly configurable to meet a variety of user needs.
- The few large firms providing pivotal applications (Documentum and SAS) or integrated suites of products (Oracle) have a "trusted advisor" role in serving the pharmaceutical industry as long as they do not abuse their position with unsubstantiated claims or noncompliant products. On the other hand, smaller companies may provide point solutions (or even somewhat integrated suites of products), but are evaluated closely before large pharmas will make significant investments. To gain trust, an integrated solution vendor will need a strong partnership strategy for integration with these pivotal applications.
- Widespread adoption of solutions is complicated by the lack of clear standards and a varying acceptance of technology and process changes by clinical investigators.

There is a lot of development to be done on the part of vendors as the market for these solutions matures. Vendors willing to accept the risks have a strong upside potential for revenue associated with applications that meet the needs of clinical trial sponsors. Strong research into user needs, developing a clear strategy for meeting them, and having a willingness to embrace innovation should be the first steps for a vendor entering this market. Existing vendors should continue to extend product lines while retaining the flexibility to meet a wide spectrum of user needs.

LEARN MORE

Related Research

- *Survey of Technical Computing Infrastructure and Requirements in Drug Discovery and Development* (IDC #29554, June 2003)
- *Worldwide Life Sciences Forecast Update, 2003–2007* (IDC #29353, May 2003)
- *Oracle: Sustaining a Commitment to the Life Sciences Vertical* (IDC #29322, May 2003)
- *Current FDA Thinking on 21 CFR Part 11: Effects Upon IT Vendor Strategies* (IDC #29020, March 2003)
- *Leading Indicators in Life Science: Clinical Trial Segment Reports* (IDC Ongoing Multi-Client Study, November 2003 and March 2004)

Glossary of Acronyms

TABLE 4

Glossary of Acronyms

Acronym	Definition
AER	Adverse event reporting
BLA	Application for the approval of a new biological
CBER	FDA's Center for Biologics Evaluation and Research
CDER	FDA's Center for Drug Evaluation and Research
CDM	Clinical data management
CFR	Code of Federal Regulations
21 CFR 11	Title 21 of Code of Federal Regulations, Part 11 — Section of CFR that contains regulations pertaining to the FDA and specifies requirements for electronic storage and transmission of data (see FDA information at www.fda.gov/ora/compliance_ref/part11/.)
cGCP	Current good clinical practices
cGMP	Current good manufacturing processes
CIOMS	Council for International Organizations of Medical Sciences (international body that oversees ethical considerations in clinical trials)
CMS	Centers for Medicare and Medicaid Services

TABLE 4

Glossary of Acronyms

Acronym	Definition
CRA	Clinical research associate
CRF	Case report form
CRM	Customer relationship management
CRO	Contract research organization
CSDD	Tufts Center for the Study of Drug Development
CTMS	Clinical trial management systems
CTS	Clinical trial supplies
DMS	Document management system
E2A, E2B, E2C	European regulatory documents on clinical safety data management
eCTD	Electronic common technical document
EDC	Electronic data capture
EDMS	Electronic document management system
EMEA	European Agency for Evaluation of Medicinal Products
EPD	Electronic patient diary
ERP	Enterprise resource planning
EU	European Union
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act (Kennedy-Kassebaum Act)
IB	Investigator's brochure
ICH	International conference on harmonization of technical requirements for the registration of pharmaceuticals for human use
IND	Investigational new drug application
IRB	Institutional review board
IRM	Investigator relationship management
IT	Information technology
IVR	Interactive voice response
LIMS	Laboratory information management system

TABLE 4

Glossary of Acronyms

Acronym	Definition
MedDRA	Medical Dictionary for Regulatory Activities (published by Northrup Grumman and used as a common vocabulary for reporting adverse events)
NDA	New Drug Application
NIH	National Institute of Health
ORPA	FDA's Office of Research and Project Administration
PHI	Protected health information (under HIPAA)
PRO	Patient reported outcomes
PSUR	Periodic safety update report
SCM	Supply chain management

Source: IDC, 2004

Conclusion

Clinical trial performance and data will remain the central piece of regulatory submissions to market in the United States. As the burden increases on sponsors to be more effective with restricted resources and time, integrated tool sets that enable cost-effective performance of these studies will be seen as necessary, and those vendors able to deliver and support those tools will be valued. Innovation will still be driven by small, entrepreneurial firms, but large pharma firms will look for established, robust organizations that can provide the assistance needed to bring clinical data to regulatory agencies faster and less expensively.

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