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Implementing Electronic Data Capture to Achieve Maximum Value

"EDC is EDC."

"We can't take the risk of losing data."

"We keep trying EDC, but it never does much for us."

"EDC is too much work for too little return."

These views on electronic data capture (EDC) are not uncommon in the pharmaceutical industry. EDC technology has been available for many years, and experience with it has produced very mixed results. Yet there have been significant changes in EDC, and major shifts in the market environment for pharmaceuticals. Intrasphere believes it is time for the industry to reconsider the potential of electronic data capture.

The pharmaceutical industry today faces extraordinary economic pressures, while developments in clinical research and technology present it with significant potential opportunities.

Shareholders expect the industry to maintain a rate of return of over 20 percent, as it has over the last five years. Total market size is increasing, but at a decreasing rate[1]. The cost of developing new drugs is increasing more rapidly (11 percent per year) than sales growth (six to eight percent annually)[2]. Mergers have not provided lasting cost reductions, and market share of merged companies has in many cases fallen from the initial combined level[3]. Given social and political concern over industry pricing, revenue increases will need to be based primarily on new drug development and increased unit sales.

Pricewaterhouse Coopers states that if research and development spending is to rise in line with projected industry sales, the largest companies will need to achieve tremendous increases in research and development productivity or "ensure that every drug they produce is a billion dollar blockbuster." They estimate that the industry will need to reduce the cost of drug development by 20 to over 40 percent[4]. It is clear that the pressure to control the costs of clinical research and accelerate time to market is extraordinarily high. And pharmaceutical companies need to achieve this in an environment where the number of clinical trials per New Drug Approval has more than doubled in the last 17 years[5].

At the same time, converging developments in research and technology create unprecedented opportunities for organizations that can respond[6]. Among these are:

- *The deciphering of the human genome and the rapid maturation of the disciplines of genomics and proteomics. These will provide new targets for drug development and the prospect of drugs tailored to the needs of much smaller groups.*

- *Technology innovation such as high throughput screening (HTS), and combinatorial chemistry, which will, in the short-term, produce peak levels in the number of new substances moving into pre-clinical and clinical testing.*

- *The promise of "in-silico" testing to focus clinical trials on compounds "most likely to succeed" in clinical trials.*

These innovations will reduce the size of trials, but increase their number, at least until the full promise of in-silico analysis is realized[7]. This market environment is pressuring the pharmaceutical industry to obtain the maximum possible advantage from use of technology, including electronic data capture (EDC), in drug development[8].

This briefing presents the rationale for pharmaceutical companies to re-explore EDC at this time, and presents Intrasphere's action agenda for successful implementation of EDC.

EDC Now Has Potential to Address Critical Industry Needs

Clinical trials are the most expensive and critical part of drug development, and EDC has the potential to significantly decrease time to market and clinical trial costs. Pricewaterhouse Coopers estimates that EDC and similar advances can bring the cost of clinical research down 20 percent[9].

During the almost two decades that EDC has been available in some form, pharmaceutical companies have repeatedly dipped their toes into its waters, but have been reluctant to seriously commit to it. They have been concerned about both the capabilities of the technology and the capacity of the EDC vendors.

The result is a cycle of "perpetual piloting." EDC is tried without adequate planning or preparation. Results are not properly measured. Benefits cannot be clearly established, and there is a reluctance to commit to the technology. However, as this wheel has turned, technology and vendors have evolved. It now seems that EDC has reached an evolutionary stage at which it is prudent for a pharmaceutical company to make a more significant investment and properly determine its full potential to the company.

EDC has come a long way:

- *Evidence suggests the technology could have significant value if it were more broadly applied.* EDC is currently used in only a small percentage of clinical trials (about 10 percent)[10]. These trials have not been structured as studies that would prove or disprove the efficacy of the approach. However, there is data that strongly suggests its potential.

  In one use of EDC, the cycle time on case report forms was reduced from 45 days to 9 days. Transcription errors were eliminated, and data errors were detected almost immediately, allowing for early intervention[11]. In another case, the database was actually locked on the day of the last patient visit, rather than the more typical three to six months afterwards[12]. Multiply that times the average 68 trials per NDA, and the possibilities for reducing time to market are clear.

  EDC reduces the time that the sponsor and investigator normally spend on transcription errors, out of range data values, and similar problems. This frees the clinical research associate to focus on source documents verification, regulatory compliance, and building relationships with site staff. Earlier data cleanup also allows for quicker and better decisions on whether to continue, expand or discontinue a study.

- *Technology has evolved.* EDC technology has improved dramatically since its introduction in the early 1980s. The earliest DOS-based systems were not robust in functionality or standardization and could not meet the industry's high standards of validity. It took months to create a system to export data from a vendor's proprietary database format to the standard database used by a pharmaceutical company. In fax-based systems, the investigator's staff faxed CRFs to the sponsor, where they were entered by the standard double-key data entry method, or scanned for Optical Character Recognition (OCR). OCR proved to have an unacceptably high error rate for this application.

  Windows-based operating systems included store-and-forward systems and client-server systems. In the earliest iterations of store-and-forward, updates were mailed to the sponsor via floppy disks or other media. These approaches produced a lag in entering data in the central database. Later iterations used an e-mail metaphor for data transactions. These precursors to web solutions reduced the lag time problem, but brought issues of security, replication and database synchronization. The pen-based data entry systems explored in this generation of EDC were too hard to use and were not found accurate enough for industry needs.

  Current generation EDC applications use the web for data transactions, whether data is being entered online or offline. Web applications benefit from robust operating systems like Windows NT managing sponsor web servers and Java-enabled virtual machines. Enterprise-wide solutions like Oracle and Oracle Lite minimize issues such as data replication and database synchronization. The Internet is an increasingly effective and secure mechanism for data transactions, information sharing and collaboration, and is viewed as such in other demanding industries like the securities business. This current generation of EDC should move the technology past the critical early adoption stage and into the early majority.

  New technologies in the works offer the potential of a true paperless clinical trial. The wireless networks now becoming available have the same performance and throughput as their wired predecessors. As voice recognition software advances, it will be combined with a wireless network to allow for the process to truly change at the investigator site. Technologies such as Bluetooth, which offer wireless connectivity between all types of devices, will allow participants to work without having to be "plugged in." When converted to clinical solutions this technology will increase the utility of EDC applications.

- *Vendors have grown in scale, stability and reliability.* In past years, major pharmaceutical companies worried that EDC product providers were small businesses, not stable or large enough to support global clinical development requirements. There are still many "me-too" companies trying to penetrate the EDC market.

However the business profiles of the established EDC vendors are better than ever before and superior to those of the new players. In addition, the two primary database management systems (DBMS) providers are both offering EDC "front ends" to their extensive installed base of enterprise database management systems. They are well positioned to challenge other EDC providers as their technology matures - a process that takes about three years of real world experience. The combination of clinical data management with EDC may make for a more attractive annual revenue profile.

EDC vendors have yet to achieve the business profile to meet the needs of a global drug development enterprise performing up to 1000 clinical trials per year. However, the viable EDC providers are certainly appropriate for the mid-tier, biotech, and academic market space. Top tier pharmaceutical manufacturers can develop their own systems, (with the same three-year maturation period, post-release, as a vendor's product), or provide the support required to make one of the viable EDC vendors an acceptable partner. With a good vendor assessment process in place, focusing on the known providers of EDC technology can yield a successful business relationship.

- *Most companies have some experience with EDC and are planning to increase its use.* More than 75 percent of the respondents in a CB Technologies survey had significant experience in clinical trials, performing more than ten per year. Two-thirds have used EDC, and sixty three percent indicated that their experience with EDC had been either neutral or positive[13]. The ACRP (Association of Clinical Research Professionals) found in a survey focused specifically on EDC that the companies of 49 percent of respondents had employed EDC systems or processes. Close to 80 percent of respondents who had used EDC indicated that the overall experience was either neutral or positive[14]. ACRP's annual survey found 66 percent of sites, 60 percent of clinical research organizations (CROs) and approximately 50 percent of sponsors expected to adopt electronic case report forms (eCRFs) within the next two years[15].

An Action Plan for Achieving Maximum Value from EDC

EDC systems and vendors may never reach a stage at which pharmaceutical companies are totally comfortable. Despite this, market forces dictate that these companies make the commitment to achieving maximum feasible value from EDC.

Based on our knowledge and experience, Intrasphere has identified a five-step process to achieve this value from EDC:

Process to Achieve Maximum Value From EDC

- *Handle implementation as a change management process, not just a new technology*
- *Get top management support*
- *Conduct an in-depth vendor assessment*
- *Select the right technology option*
- *Integrate with other systems throughout the company*

1. Handle implementation as a change management process, not just a new technology

EDC implementation must be handled as a change management process, affecting primarily the clinical research division, but also having an impact on other divisions. Implementation cannot be solely an IT responsibility.

Some pharmaceutical companies have used paper methods to collect clinical trial data for more than a century. The procedures and methodologies are intimately familiar to clinical research departments, CROs, and many investigators — paper methods are simply "the way things are done." Where electronic approaches are used in only a small number of trials, the electronic process is unconsciously retrofitted to its paper process equivalencies, minimizing cost savings.

In this kind of environment, EDC can succeed only by making the key stakeholders participants in shaping the EDC solution. Consensus development will ultimately have more impact on what the company can achieve than the timetable for deploying hardware. While the technology clearly needs to work within the constraints of an industry that is highly regulated, multinational, and requires absolute security, technology itself may represent only 25% of the overall solution.

First, assess the needs of the internal organization (Figure 1). The guiding committee should represent the major internal constituencies, including data and trial managers, clinical data analysts, field research coordinators, IT professionals, and when appropriate, external users including investigators, coordinators and representatives from preferred contract service organizations (CSOs). The committee's responsibilities will include development of a communication plan that will keep each constituency involved and informed about the decision-making process and specific decisions being made about EDC, through internal presentations and discussions, interviews, focus groups and internal newsletters.

Figure 1: Change Management - Internal Needs Assessment

Assessment Element	Examples
Stakeholder Requirements	- Monitoring and reporting tools - Online/offline data entry (or both) - Access - Cultural or logistical issues - End-user qualification and training
Financial and resources Commitment	- Preferred form of license. e.g. enterprise, product, therapeutic category - Costs for technology knowledge transfer and/or vendor services - Cost ramifications of implementation, maintenance, etc
Risk profile - risk management plan	- Security requirements - Password administration
Process analysis	- SOPs, WPs, BCPs
Business rules Analysis	- Dataflow, workflow
Technology integration objectives	- Short and long-term integration requirements: - Clinical database management system - SAS datasets - Electronic regulatory submission - Finance - Project management/trials management
Fit with broader technology strategy	- How planned implementation of other technologies in the division and company will affect the requirements for EDC
Buy-build Assessment	- Analysis of vendor offerings - Customization/optimization capabilities - Cost and time - Time to mature application

The importance of involving the investigators and their staff in the planning process in some way cannot be overstressed. An apparently ideal EDC design will fail if it does not take into account, for example, that some users' experience with technology is limited to a few months use of e-mail.

Business process change is part of change management. Typically, EDC technology has been implemented with minimal attention to design for integration with other business processes. Business process change requirements in the internal and external environments include:

- *Modifying Standard Operating Procedures and Work Processes:* Trying to fit a new EDC system into the Procrustean bed of current SOPs will result in frustration, inefficiency, and opportunity costs.

- *Re-evaluating Business Continuity Practices:* Disaster recovery requirements will vary tremendously with the type of EDC system. Planning for the appropriate contingencies is part of the implementation process.

- *Pilot program:* A successful pilot program includes a pre-determined metrics analysis plan, willing and interested participants, and realistic expectations with a "next steps" plan in place:

  -*Metrics analysis:* EDC implementations usually have not included adequate processes to measure the results achieved or have not specified criteria for determining success in advance. For instance, while macro measurements such as time from last patient visit to data lock represent a long-term benefit, these kinds of measurements cannot realistically be made while experimenting with something so completely different from the norm. Short-term measurements may need to focus on reductions in the number of error correction transactions, the rapidity of central data access, or issues of usability.

  -*Best test not just stress test:* The EDC/paper-based system comparison must be a reasonable one. Allowance must be made for the learning curve with any new system in designing appropriate metrics. Conditions in investigator's offices may be less than optimal for new system implementation. The idea is to compare paper systems with the best possible approximation of how EDC will perform as a "steady state" system, not a brand-new one.

  -*"Next steps plan" in place:* Once it is determined whether the pilot was a success, appropriate next steps may include options such as a direct comparison between EDC and the paper process — measuring differences and extrapolating the value that the new technology might bring if truly integrated. Alternatively, the technology could be rolled out across a number of studies to expand the metrics analysis to include a broader array of variables.

The results of the needs analysis, the business process requirements, and the technology plan (see below) must be combined to produce a comprehensive implementation plan that addresses all aspects of change needed to maximize value from the EDC system.

Implementation Plan Elements

- *User adoption tactics*
- *Training for the various stakeholders*
- *User documentation requirements*
- *User process-readiness evaluation*
- *User-specific issues*
- *Helpdesk solution - internal, subcontractor, vendor*
- *Technology administration*
- *Hardware qualification and procurement*
- *Hardware management/Asset management*
- *Hardware maintenance*
- *Password management/security*
- *Reporting*
- *Metrics analysis - measuring success*
- *Cost effectiveness, cost benefit, cost analysis*
- *Decision support analysis*
- *User satisfaction analysis - user adoption feedback*
- *Time-investment paradigm*
- *Change control*

2. Get top management support

Executive support is critical to the success of an EDC implementation effort, as are financial commitment, necessary resources and substantial attention to people and process. To realize full worth from EDC, that system must help turn raw data into information and enable simple, in-depth access to the data for the system's various constituents. In most instances, both the non-permeable nature of the pharmaceutical company's departmental structures (the silos), and the use of paper systems to support clinical research are deeply entrenched. Only executive commitment to EDC and the process involved in implementing it can move people beyond organizational inertia to the active involvement required.

3. Conduct an in-depth vendor assessment

Once a corporate perspective has been established, there will often be a decision to work with a vendor for at least some part of the EDC solution. Even where the decision is made to "build" rather than buy, a partnership with a vendor may provide for a quicker or more reliable way to create a piece of the architecture.

The vendor assessment process should address those categories listed in Figure 2.

Figure 2: Vendor Assessment, Key Criteria

Category	Examples of Criteria
Business profile	- Years in business - Corporate partners - Number of employees/offices
Financial stability	- Ownership - Financing - Current and historical profitability
21 CFR Part 11 Compliance	- Compliance with FDA requirements for documentation, training, security and auditability
Domain knowledge	- Knowledge of clinical trials - Familiarity with industry regulations - Users perspective
Experience	- Type of customers (e.g. size, sector) - Number/geographic scope of trials in which technology has been used - Accumulation of metrics - Deployment strategies
References	- Overall customer satisfaction - Ease of implementation/meeting timetable - Smoothness of update process
Support, helpdesk	- Coverage for investigators in all time zones - Helpdesk software and policies - Escalation policies - Staff experience - Multiple language capabilities
Pricing	- Pricing algorithms--per investigator, per data point, per installation, per trial? - Annual contract vs. project-based approach - Hidden costs
Customization and optimization	- Modularity for simple customization - Technology's capability to support customization - Willingness to customize or optimize
Future development plans	- Planned upgrades, release frequency - User input - Compatibility with previous releases. - Plans for new system architecture
Ancillary tools	- Reporting tools (Crystal Reports) - Local client database (Oracle Lite)
User interface/ease of use	- Interface intuitive for investigators - Menu systems where appropriate - Easy to move between fields - Acceptable response time
Integration profile/configuration requirements	- Data flow - APIs - Data extraction or bi-directional interface with internal systems

Members of the assessment team will need the following kinds of experience and expertise:

- *A broad understanding of the business requirements that the system must meet*
- *Strong knowledge of available technology options related to legacy platforms and other pending technology change decisions*
- *The ability to evaluate a vendor's market and financial position*
- *Knowledge of the historical experience with EDC*
- *Familiarity with the investigator office environment from both an operations and technology perspective*
- *A deep understanding of systems issues, including interfaces, communication, integration, implementation, and support for end users and sponsors*
- *The interviewing skills required to obtain more information than a reference intended to provide.*

New EDC vendors may offer pricing opportunities or "cutting edge" technology that looks attractive to mid-tier pharmaceutical companies and smaller clinical research and development companies. Pursuing these opportunities may be risky. The newest "EDC provider to watch" usually has an unstable business profile and is at significantly increased risk of failure.

Figure 3: Currently Viable EDC Architectures - Advantages and Disadvantages

Architecture	Features	Advantages	Disadvantages
Store-and-forward	Software and local database are on investigator PC. Site data is periodically sent to central site as e-mail attachment, and then uploaded. May also use third party communication packages (e.g. Xcellenet, CrossTalk) to transfer data increments.	Most consistent performance to the user. Since application and data reside on local PC, user performance is controlled by the power of their PC.	Usability of these Windows-based applications varies widely. Because the application executes on the PC and the data is local, the PC must be validated and the computer and data must be secured. Investigators running multiple trials will have a separate PC for each trial
Client/server	Client software on investigator PC is tied to applications on the sponsor's server computer via a middleware communication link. Requires all components to be online at all times.	Because application is local to the site, response time is generally quick. If the application needs to retrieve data it will perform like a typical web application. Since data is maintained on the sponsor's server, the site does not need to worry about the security of the local system.	Local applications must be distributed to the sites. This can be done via electronic download but will be a slow process due to file size. Changes to the protocol may require shipping a new application to the sites. Additionally, because the application executes on the PC, it must be re-validated. Sites running multiple trials will need a separate PC for each trial.
Web-enabled	Web-enabled systems start with either a store-and-forward or client/server architecture and present the user interface over the web. Most of these systems use the web as the communication link in a wide area network (WAN).	Easiest systems to validate and deploy. Easiest to update since the application and data resides on the central server. Additionally, these systems are considered the most secure.	Require a constant network connection for all activities. System performance is directly related to Internet speed. Also, since web-enabled systems were not designed to execute on the web, performance can be erratic.
Web-based	Web-based systems use the investigator PC solely to enter data to a database on the sponsor's server. True web systems are built completely in the native language (e.g. HTML, Java, XML) of the web. These systems can be accessed via the World Wide Web with a standard web browser.		

4. Select the right technology option

A data system architecture is a framework for how all the components of a system fit together. In an EDC system, the architecture is the hardware and software that allows clinical personnel to execute trial tasks following their standard operating procedures and process flows. The needs analysis will drive the criteria for evaluating the alternative EDC system architectures and determining which is the best fit with an organization's requirements. The hybrid model, a combination of the client/server and web solutions, is currently popular because it allows investigators, coordinators, and clinical research associates to work "unplugged" and in batch mode, but allows for ease of connectivity and potentially rapid access to data.

Web systems have many advantages, including ease of validation, deployment, and updating. Their most obvious limitation is Internet transmission speeds and barriers to connectivity. These will disappear over time (as bandwidth increases and Internet access improves). However, physicians, nurses, coordinators, and field-based clinical research professionals experience "needing to be connected" as a limitation on their work. When wireless technology becomes a viable option, it will allow your investigators to work "online" while still remaining "unplugged."

As Figure 4 indicates, web-based systems are in many ways simpler to administer than web-enabled systems. The complexity of a web-based system arises from the need to provide an always-on connection to each investigator's office. For example, DSL connections are not available in all geographic areas, and even where they are, the installation process is notoriously cumbersome.

Figure 4: Comparison of Web-Enabled and Web-Based EDC Systems

Feature	Web-Enabled Systems	Web-Based Systems
Computer Requirements	A dedicated computer required for data entry with very specific requirements at the investigator site	Almost any computer (with basic requirements) and a web browser can be used for data entry Small amounts of site administration required, mostly at start-up
Site Administration	Site administration required for back-up of data and handling of the PC is required	Small amounts of site administration required, mostly at start-up
Data Security	Local data is stored on the PC hard drive and is at risk of theft and/or system failure	All study data is stored on a central server, so there is no local data to protect
Requirements if a computer fails	Replacement computers must be sent to sites	Easier to replace
Constant online connection to central server	Not required	Required
Central database up-to-date?	Not always	Always
Protocol amendments synchronized to application?	Not automatically synchronized to PC	Changes made automatically on the central server
Where application logic executes	Primarily on the client computer	Primarily on server computer

5. Integrate with other systems throughout the company

An EDC solution cannot be approached in a vacuum. The initial data collection aspect is critical. However, the real obstacle is integration with existing legacy and enterprise systems. These "legacy systems" are often disparate or component driven and can be home grown solutions or third party products. Clinical data is powerful when integrated with the clinical data management system (CDMS), laboratory data, coding tools, safety, drug supply, financial, and electronic regulatory submission (ERS) technology. Naming conventions, primary keys, subject identification numbers, file types and database structures, are a few core considerations that must be addressed in the "front end" of the process. Requirements for technology integration are identified as part of the needs analysis and evaluation process.

Integrated systems and custom development services are driven by skills and fluency in a wide range of hardware platforms, operating systems, database architectures, network topologies, languages, communications protocols and security standards. Some of the technologies may include XML, Java, DHTML, COM, Oracle and WAP. An integrated solution needs to deliver a consolidated high-level view of clinical trial information to a wide variety of stakeholders across the drug development enterprise. It should allow an "executive dashboard" view of data.

Executive Dashboard Elements

- *Subject enrollment information*
- *Clinical database management system (CDMS) including discrepancy management*
- *Financial data, and cross-project and cross-group comparisons*
- *Ad hoc reporting capabilities*
- *Access to external links*
- *Competitor information*
- *Document management*
- *Product information*
- *Safety trend reporting*
- *Organizational structures*
- *Resource utilization*
- *Regulatory and governmental policies*
- *Internal standard operating procedures*
- *Manufacturing and packaging*
- *Meetings and events*

With years of infrastructure (legacy systems) already in place, how can the data from EDC systems be integrated into the backend of the process? Prior-generation EDC products had to be retrofitted to existing internal technology architecture and could not be integrated with the solutions of other technology vendors. In contrast, third-generation products are flexible, parameter driven applications that can be tied in to a company's other technology infrastructure and integrated with the products of other vendors.

While vendors tend to assert that integration is no problem, Intrasphere's experience is that with any system, integrating data from the EDC system takes a lot of effort and time. Fortunately, some systems do make it easier than others:

- *Third Party Products:* The internal databases of the two major clinical data management systems, Oracle Clinical, and ClinSoft's Clintrial, are well known by EDC vendors and sponsors and are somewhat standardized. However, since each company customizes these products to its own needs, it is still ultimately difficult to integrate the EDC data.

- *Legacy Systems:* Data is imported into existing legacy systems using floppy disks, Zip disks, writable CD's, and other media. A wide variety of file types and formats are in use, including SAS datasets, ASCII files, database files, and portable document format (PDF). These approaches will continue until a true standard is realized.

- *CDISC Initiative:* The Clinical Data Interchange Standards Consortium (CDISC), a group comprised of software vendors and sponsors, has proposed a standard way to exchange all types of clinical data. The first version of the CDISC submission metadata model was released last year. Once a version of this standard is approved by the industry, vendors will be able to produce a standard transfer file that can be read by any CDISC compliant system.

A methodical analysis and a comprehensive plan are key to keeping critical integration needs from surfacing after contractual obligations have already been defined and the project scope finalized. The challenge of integration is to balance overall business processes, workflow requirements, and "legacy" source systems, with the EDC product and vendor requirements.

Conclusion

Achieving maximum value from EDC requires a new and more comprehensive approach to its implementation. Top managers must motivate a change management approach that addresses the entire spectrum of business processes in the clinical research division, and involves the major internal and external stakeholders. Those participating in the planning process will need to learn about the options for EDC systems architecture, and determine which alternative appears likely to maximize results. Careful consideration must be given to the "build vs. buy" decision, and whether vendors should be utilized. The task in vendor evaluation is to find a best fit among established EDC vendors and determine what relationship will provide the best obtainable level of comfort. Lastly, in today's climate knowledge management is a core competence for pharmaceutical companies. Maximizing value from an EDC system requires that it be integrated with existing and planned information systems, to build an information-rich environment for business operations and decision-making.

Footnotes

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