Accelerating Drug Development with an Integrated Electronic Approach

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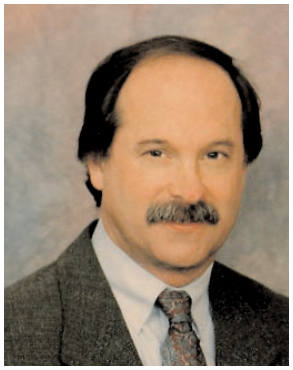

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Clinical testing of new drug candidates is an increasingly complex, lengthy and expensive process with a dauntingly expensive price tag: clinical testing alone now costs more than US$100 million, with large scale pivotal (Phase III) studies generally costing between US$2 and US$30 million each.

The increased cost of large scale clinical evaluations reflects a number of changes in the industry. Firstly, pivotal studies are considerably more complex than they used to be. For example, over the past decade, the amount of clinical information in a regulatory submission has more than quadrupled. Clinical evaluation now averages more than 5,500 patients, each of whom undergo more than 65 procedures each. Secondly, increasing globalisation of markets means that studies include more countries, cultures, languages and regulatory requirements. Finally, there is an increasing awareness of the value of time in the development process: each day's delay in getting to market after filing patent application is estimated to cost US$1 million in lost revenues. Against this backdrop of increasing expenses, an increasingly efficient means of identifying and screening new compounds means that development pipelines are increasing.

Companies developing pharmaceutical products thus face mounting pressure to increase the efficiency of the clinical evaluation process. The other side of the research coin – time and resources spent pursuing drugs that do not make it to market – can also be costly, particularly to smaller companies without an income stream. A month's delay in even a modestly successful drug – say, one that sells US$200 million each year – means nearly US$20 million lost. One reason for high development costs is the fact that only a minority of drugs that enter clinical testing ever make it to market. Even late in the process, the mortality rate remains high – only about one quarter of drugs entering Phase III eventually make it to market.

The structured, predictable nature of clinical data lends itself to information technology, as witnessed by the recent proliferation of products offering electronic solutions. However, successes at achieving bottom line economies in time or costs have been inconsistent. The fact that drug development times have increased recently suggests that a quantifiable benefit has been difficult to demonstrate. To some extent, this limited success reflects some companies

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experiences as growing pains, likely from any new technology, particularly in that it operates in a rigidly structured regulatory environment.

WHY HAS A BOTTOM LINE BENEFIT BEEN ELUSIVE?

Perhaps the most important reason is that many solutions, including the vast majority of those offered today, represent only partial solutions that are difficult to integrate into existing procedures, policies and systems. For example, even a superb system to collect data at a clinical site will prove to be of minimal use if quickly collected data waits in queue for entry and validation. This lack of integration obviates the advantages of most current offerings. Software may also be difficult to use because of inflexibility, inadequate product support or poor design. A common deficiency is an inadequate consideration of how products interact with other existing systems, particularly those that are used in clinical sites.

Faced with the need for more efficiently performing clinical evaluations of drug candidates while reducing timelines, we have developed an integrated electronic system that covers the time from when a drug is first used in man to the submission of regulatory applications. Technical descriptions, as well as the system's capabilities for early stage (entry in man through Phase II) development, have been described previously, so this article focuses on the system's capabilities for later stage clinical evaluations and multiple regulatory submissions.

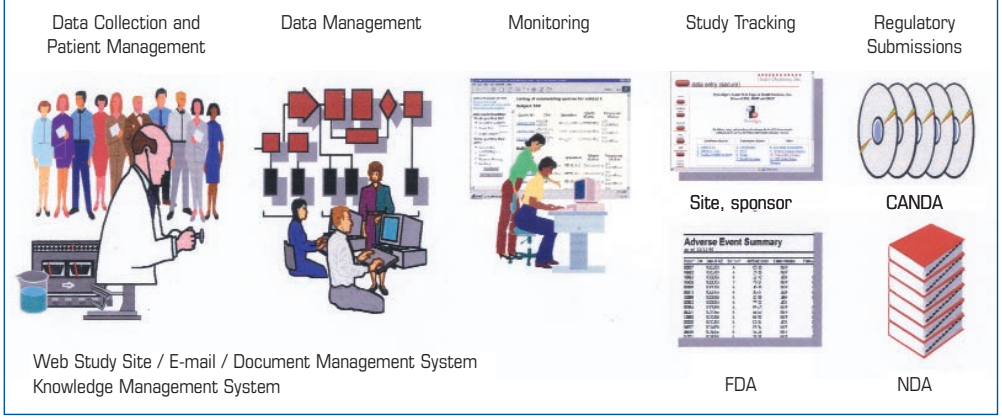
The main difference between this and traditional systems lies not only in its ability to effectively deal with a number of processes, but to make the research process an adaptive one that is based on a stream of information, both qualitative and quantitative, coming in from the field. Where traditional systems have required completion of one phase in order to move to the next, this approach both accelerates existing tasks and allows many to be carried out simultaneously. This capability is based on being able to collect, validate and disseminate information virtually as it is collected, much more quickly than in the past, due to advances in information technology and communications coupled with careful planning and execution.

THE SYSTEM

Our approach includes five basic components, each of which is linked with enabling technology (see Figure 1). These are:

- Data collection and patient management – entry of clinical measurements, observations, and laboratory information, in addition to administrative functions such as tracking study supplies, randomisation and patients scheduling
- Data management – making sure that data are error free, including site queries as needed
- Site monitoring – assuring accuracy of data, compliance with good clinical practices and the absence of fraud
- Status tracking – monitoring study progress and quality for the sponsor, internal checks and regulatory groups
- Regulatory submissions – preparation of multiple submissions to licensing authorities

Figure 1: Health Decisions' Integrated Electronic System for Clinical Evaluations



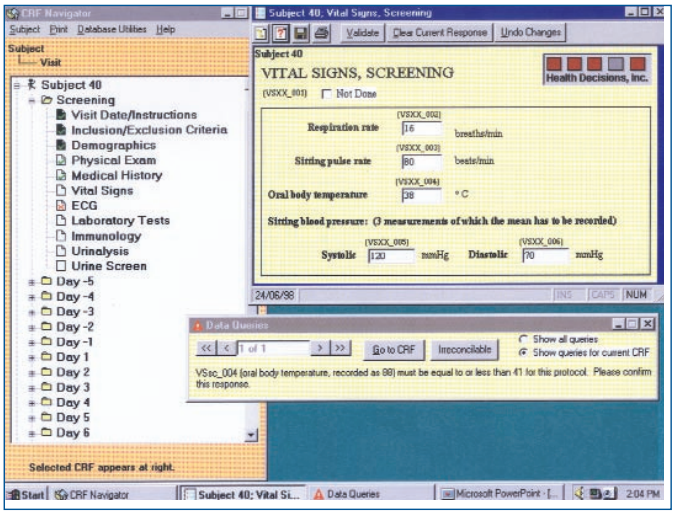


Figure 2

Each component is individualised around the specific requirements of each study, including sponsor and administrative requirements. Communications form a foundation for the entire system. The Internet is used extensively, from data collection to query resolution, to dissemination of study progress reports. Also included is a study knowledge base, which authorises a user to access all information relevant to a specific question. For example, asking about handling a serious adverse event (SAE) might produce a list of choices that includes federal regulations, how to contact the responsible medical monitor, how similar SAEs has been handled in the past, and initiate filing of a new SAE. New information, such as responses to questions, is continually added to the knowledge base. This capability provides multilingual support on a 24 hours a day, seven days a week basis. One of the strongest benefits of this system is its ability to easily link team members throughout the world when decisions are required, and to allow the freedom of on demand access throughout multiple time zones.

DATA COLLECTION AND SITE MANAGEMENT

Site events are divided into data collection and study management, both of which are included in our integrated system. Data are collected either by electronic CRFs (see Figure 2) or machine readable paper forms (see Figure 3). Since both e-CRFs and paper CRFs can be used concurrently in the same study, which are used at each site depends on the capabilities and desires of each site. Use of e-CRFs allow rapid dissemination throughout the world in multiple languages, since printing and shipping are not required. This system also has the capability to quickly switch between languages. Forms can similarly be updated electronically and transparently to the user.

A prime advantage of e-CRFs is that data can be validated as it is entered. With errors detected in real-time, corrections can be made with the

Figure 3

VITAL SIGNS 34

Investigator

Patient Initials

First / Middle / Last

Randomisation No.

THE EFFICACY, SAFETY, AND TOLERABILITY OF LAZABEMIDE (Ro-19-6327) VERSUS PLACEBO ADMINISTERED FOR ONE YEAR IN PATIENTS WITH PROBABLE ALZHEIMER'S DISEASE
Protocol Nos. PDL 1000p and 1001p

Is This Now: ①Screening ②Baseline ③Week 4 ④Week 9 ⑤Week 17 ⑥Week 26 ⑦Week 39 ⑧Week 52 ⑨Week 54 ⑩Unscheduled Visit
VSxx_001

Date		
Month	Day	Year
Jan ①		
Feb ②		
Mar ③	00	00
Apr ④	11	11
May ⑤	22	22
June ⑥	33	33
July ⑦	44	44
Aug ⑧	55	55
Sep ⑨	66	66
Oct ⑩	77	77
Nov ⑪	88	88
Dec ⑫	99	99

VSxx_002 **Vital signs done?** ①Yes ②No

Measurements will be made after patient has been in supine position for 3 minutes. Patient will then sit up.
Measurements will be repeated after patient has been sitting for 1 minute.

SUPINE

VSxx_003	BP (mmHg)	
Pulse	VSxx_004	VSxx_005
(bpm)	Systolic	Diastolic
000 111 222	000 111 222	000 111 222

SITTING

VSxx_006	BP (mmHg)	
Pulse	VSxx_007	VSxx_008
(bpm)	Systolic	Diastolic
000 111 222	000 111 222	000 111 222

patient present. The short feedback loop also allows errors to be quickly identified and corrected. Use of e-CRFs also does not require the computer to be connected when data are collected. This allows flexibility in both when and how patient interviews and examinations are conducted: a laptop can be carried from room to room, and the interview can be interrupted if necessary. e-CRFs are also included as part of a study management module that can also print laboratory slips, perform randomisation, track study supplies and other administrative functions. The system may optionally be expanded to include patient scheduling and other administrative functions, particularly as they tie in with existing electronic systems.

At the end of each day, the computer is connected to the Internet and automatically uploads data to offices. Optionally, information collected during the day, along with parameters specific to a study or site such as time required for interviews, number of errors corrected, and other metrics, are uploaded; study queries and other communications are simultaneously downloaded.

A second option for data collection is the use of machine readable paper forms. All CRFs are validated the day of receipt, a critical capability made possible by machines that read more than 1,000 forms per hour. In some circumstances, we have received as many as 5,000 forms in the morning and processed all forms before the end of the day, with a data processing staff of five.

A study management module provides the additional capabilities of scheduling patients, tracking study supplies, printing laboratory slips, and other administrative functions. Randomisation and other statistical capabilities can also be included but are generally done only if e-CRFs are used.

SITE MONITORING

Site monitoring is one of the least efficient components of conduction of large clinical trials. Typically, one-third of a study's budget is involved with monitoring, the main point of which is to assure GCP compliance and to detect potential fraud. Monitoring also helps improve study efficiency by dealing with procedural questions and resolving issues between visits. Monitoring, however, tends to be inefficient, in part because monitors spend an inordinate amount of time in non-productive activities such as travelling. and in part because the present system encourages a 'checklist mentality' that focuses more on form than substance.

A short feedback loop is central to identifying and correcting site problems. Learning about an error a day or two afterwards (or, if e-CRFs are used, immediately) is extremely effective at reducing the number of queries and procedural problems. On one study, for example, incoming information immediately revealed that a test of subtle cognitive function was not being administered correctly, and the individual involved was immediately contacted and additional training provided. Without this feedback, the same error is likely to have been perpetuated.

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This approach also changes the role of the site monitor from an individual whose primary concern is with procedural details to one more broadly involved with study management. A primary goal of this approach has been to decrease the amount of time spent travelling, to reduce the monitor's time spent in answering routine questions (handled by the Study Knowledge Base) and to increase the amount of time devoted to individualised site interactions and measures to improve study efficiency.

The clearest measure of the system's success is the marked reduction in the number of site queries and the very quick resolution of those that do occur. Database lock is generally completed the same day as the last patient visit, in part because this system can resolve queries in a matter of minutes if necessary, even by using paper forms. This capability separates closing the database from the need to physically visit the site. Site closeout visits are now only necessary for issues such as drug accountability, and they

can be conducted as a convenience rather than as a prerequisite for closing the database.

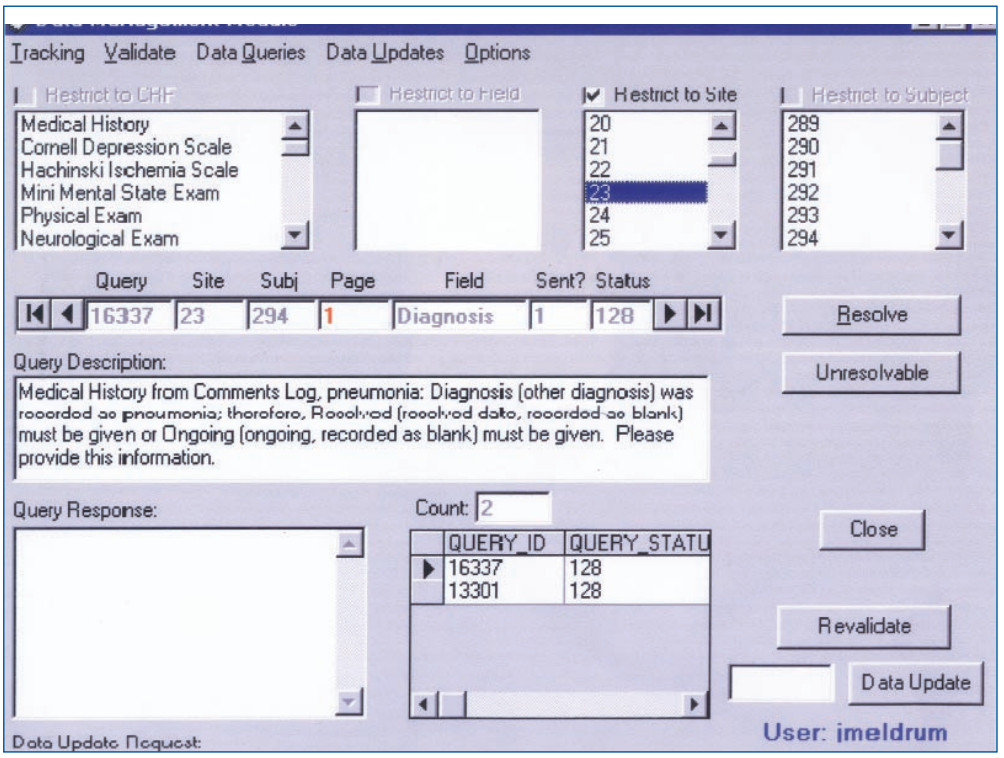
DATA PROCESSING

Data processing and validation is conducted in one of two ways, depending on whether paper or electronic CRFs are used. e-CRFs include validation as an integral part questionnaire, so each section is reviewed as it is completed. This includes not only typical range and consistency checks, but visit scheduling and longitudinal checks for indices such as measurements recorded at previous visits.

If paper is used, forms are machine read, usually some hand entry is required for open data fields, type I errors are hand checked, and queries are returned to the sites by the Internet. Validation includes internal range and consistency checks, as well as additional checks such as marked deviation from previous values. e-CRFs require only the latter stage in addition to a number of internal validity and consistency checks built into the system as part of the validation required for data integration. Laboratory data are integrated at this point, usually in the form of electronic files from central laboratories. In some cases, simple artificial intelligence is used to decide whether a query can be handled internally or needs to be referred back to the site for resolution. Queries are both transmitted to the site and responded to electronically, either through encrypted e-mail or a dedicated study website. Query generation is automatic, with multilanguage capabilities precoded according to each site's preference (see Figure 4). Queries are sent to the site, corrections entered, and the response returned. Software automatically detects the response, which is reviewed and either accepted or rejected due to the need for further explanations. Validation checks are repeated as appropriate, and the response is reviewed before being written into a database and so considered resolved. Site managers or CRAs , depending on how the study is set up, have full tools for reviewing number and type of queries as well as sorting by outstanding, resolved and other queries.

Even using relatively slow paper forms, this system has been highly successful at both reducing the number of queries generated (because of rapid feedback) and in resolving queries. For example, an Alzheimer's disease study that involved 98 sites in six countries averaged less than a day for CRF validation. Query resolution depends largely on how study sites and monitoring is established but can be performed in as little as several hours. Normally, however, such speed would be important only at study completion, and a day or even more would not be deleterious to study progress.

Figure 4



REGULATORY SUBMISSIONS

Because today's development environment is increasingly multinational, organising the thousands of pieces that comprise each document is essential. Our document management system ingests a variety of formats, including paper, electronic files, and others such as x-rays and EKGs. In some cases, submissions could also contain video or audio clips, and their inclusion is handled with similar aplomb. Linked to the document management system is a sophisticated publisher that can format, paginate, organise, produce tables of contents and print the submissions. These can be produced in paper or electronic form with equal dispatch.

The heart of this system is its web-enabled feature, which means that a submission team can work, regardless of where they are or when they work. An authorised individual can check out a document, make changes, and send it back out. The system has complete version control, access restrictions, and similar security and integrity measures such as might be expected for any internal system at a major pharmaceutical company.

Multiple submissions are made possible in part by this system and in part by careful planning. For example, inclusion of all study documents from the outset helps ensure that minor holdups such as investigator CVs or FDA 1572s are not discovered to be missing at a critical time. Notes of telephone conversations or theme threads can similarly be tracked and made available as needed. The system can reshuffle certain discrete pieces of information such as toxicology studies, add or subtract portions as appropriate for each submission, and then publish it. For example, a European submission might use clinical study reports summarised in an expert report. In the US, the same study reports can be included, but summarised in integrated summaries. Indeed, the most difficult part may be dealing with the enormous volume of paper still required by some regulatory authorities.

COMMUNICATIONS

Communications is the foundation of the system. The system has been designed at the outset and evolved around the concept that each individual involved in the study needs to have ready access to information. This information, however, must be viewed as a facilitator rather than as an end in itself: it no more substitutes for good judgement than a spreadsheet does when making financial decisions. The difference is that this system provides a wealth of information in real-time. The net effect is the capability of making earlier, better informed, decisions.

The Internet forms the backbone of the communications network. This has been established in several ways, but the most effective is simple use of the Internet using a robust system of firewalls and encryption. The encryption is designed for assuring data integrity as well as security, since both are critical. This system can be established as a virtual private network or configured to work within an existing system such as might exist at a sponsor.

Typical information tracking might include recruitment (especially if competitive recruitment is being used), queries by sites and possibly by an interviewer, and other parameters specific to the study. The latter might include tracking patient dropouts and reasons, lab values and history on patients with abnormal findings or similar. In practice, this component is both specific to a study and changes during the course of a study as additional information is desired. Similarly, however, information might be deleted if, for example, after study recruitment is completed and emphasis switches to drop out rates and reasons, possibly including issues such as retrieved dropouts. An advantage is the flexibility to incorporate components and capabilities depending on the specifics of each study, including those of the drug under investigation, sites involved, and sponsor requirements. The system can similarly be refined as the study progresses.

THE BOTTOM LINE – HOW WELL DOES IT WORK?

Performance metrics indicate a marked improvement of this approach over existing systems. For example, a current study of Alzheimer's disease that involves 1,400 patients observed for a year by 98 sites in six countries, with a 200 page multilingual CRF. Performance for this study is contrasted with industry standards in Table 1. In each case, performance on this study bettered industry standards by a substantial margin – in some cases, several orders of magnitude.

The study sponsor estimates that for the Phase III study and submission preparation, this approach saved US$30 million in direct costs and 1.6 years of development time. Use of the entire system,

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starting at entry into man with the intention of culminating with a global NDA, was recently estimated to reduce development time by approximately 50 per cent as compared to other products currently in development. From a business perspective, this capability will allow development to leapfrog several products currently being evaluated by systems that include some electronic components. The financial consequence is a marked increase in the drug's internal rate of return and net present value compared to that if a major pharmaceutical company had developed it.

"Our development efforts include ongoing evaluations of other electronic options, both in the development laboratory and with feedback from the field by other users. Although our approach includes the capability of incorporating other systems such as interactive voice response, handheld computers, personal digital assistants, and faxback items, we feel that in general, these do not produce the same degree of flexibility and thus usefulness."

COMPARISON WITH OTHER ELECTRONIC APPROACHES

Our development efforts include ongoing evaluations of other electronic options, both in the development laboratory and with feedback from the field by other users. Although our approach includes the capability of incorporating other systems such as interactive voice response, handheld computers, personal digital assistants, and faxback items, we feel that in general, these do not produce the same degree of flexibility and thus usefulness. Faxback systems, increasing in popularity in the industry recently, may offer false hopes by providing systems that are unpopular among sites. These systems are also limited by the fact that the time from receipt to data entry to validation is quite slow compared to our approach. In most cases, faxback systems utilise some form of optical character recognition, but users report long processing times for each form and multiple errors that require individual attention. Some systems even utilise double key hand entry of information, a process that manages to incorporate the most inefficient of traditional approaches.

A common limitation of electronic systems is inadequate attention to site users. Stories are not uncommon of electronic systems that prove less efficient than the system they were designed to improve upon. Many sites charge more for studies that use electronic data capture as compared to paper, and even simple faxback systems can be frustrating when inadequate attention has been afforded to the end user.

LESSONS LEARNED

As impressive as these tools are, they remain simply tools. Ultimately, it is the users that will determine how successfully they are used. Managers may make the mistake of seeing technology narrowly, in simply speeding up existing processes. Technology, however, does not so much speed up the clinical research process as redefine it.

These systems demand a moderate degree of computer familiarity, and training is a part of every study. We have found, however, that after training, the vast majority of users come to strongly prefer this system, to the point where they are reluctant to return to traditional methods. The capability of closely monitoring the performance of even individuals and sites can be used as a means of reinforcing training, with supplementation or additional training, or other resources as appropriate. Ultimately, the continuous and very quick stream of feedback markedly improves site efficiencies.

We use these systems every day, for every study we carry out. Being close to the research process and having our staff constantly using and refining these systems demands individuals with unusually broad perspective and capabilities. Similarly, a critical realisation by sponsors is that this kind of effort requires considerably closer co-operation with the CRO, including more ready sharing of weaknesses as well as strengths. The ultimate goal of the system is to reduce timelines for drug development, which means that all involved with the process must use these new tools to reassess and improve on how they work. ◆

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