Realising the Promise of Internet Clinical Trials

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The past couple of years have seen an explosion of interest in the use of the Internet to conduct clinical trials of new pharmaceutical products. At the last count, over 60 companies supplied software or services using the Internet to some degree. Invariably the supplier's aim is to dramatically reduce the time required to bring a new drug to market. These claims probably sound familiar and many readers will remember the same claims being made when various forms of remote data entry and clinical trial software were introduced a decade ago. Experience, however, has taught us that none of these approaches consistently and significantly alters the clinical development cycle time; indeed, many suffered from difficulties that actually slowed the process down and proved very expensive. Is it different this time around?

THE DRIVE FOR CHANGE

Clinical testing of new drug candidates is an increasingly complex, lengthy and expensive process with a dauntingly expensive price tag. Companies developing pharmaceutical products face mounting pressure to increase the efficiency of the drug evaluation process, particularly in the clinical stages. The structured, predictable nature of clinical data lends itself to information technology, hence the large number of entrants into the software vendor market and the surge of contract research organisations wishing to talk up their electronic clinical trial capabilities. Once again, technology is the flavour of the month with the Internet and electronic data capture (EDC) being hailed as the 'Holy Grail' in many marketing messages.

There is no doubt that as an industry we still have improvements to make in controlling the time and cost of our development process, but to see technology as the white knight riding to save us is too simplistic. The fact remains that past technology initiatives have had no measurable effect on drug development cycle time, and we are once again in danger of raising expectations too high. This leads to disappointment, disillusion and a belief that these systems can provide no real bottom line benefit.

THE PROMISE OF TECHNOLOGY

Such disillusion would be a great pity since I believe that things have evolved considerably – at least in terms of the sophistication of technology. Many of the systems currently on offer reflect a great deal of thought and innovation in their approach to clinical trials. Most concentrate on the process of data acquisition – ranging from the use of various forms of scanning or media retrieval at one end of the spectrum, to full-blown electronic data capture systems at the other. Incorporating the Internet has allowed the rapid transfer of data from the point of collection – often on the same day the trial subject visits the investigational site – to the company who can then validate and generate data queries and enter those data into the clinical trial database. Often the 'back office' processes are conventional lines with manual handling of data and data queries, but some of the newer systems integrate all the data management parts electronically (1). Some systems can use EDC, optical mark read forms or other sources of data input for acquisition, with all subsequent data handling being managed across the Internet, including data query resolution via e-mail (for those investigators without Internet access) or a secure web-based data query system (see Figure 1).

The advantages of these systems are shown in Table 1. The ability to access data collected at site only a matter of hours or a couple of days previously has clear implications for enhanced study tracking, quality assurance and site monitoring. What may be less clear is the ability to use these data to assess other qualitative aspects of the trial as it progresses, such as trends in statistical variability using pooled blinded data (indicating a quality problem with protocol adherence or site training), or drift in mean entry scores on a particular scale (indicating those patients who are only just eligible being squeezed into the trial). At the end of a trial, close-out and locking of the trial database can occur much more rapidly than in conventional trials due to the lack of those troublesome small queries. At the end of a pivotal trial programme, the decreased time from last patient observation to final study report allows earlier preparation of the regulatory submission, especially in terms of integrated summaries.

There is no doubt that current Internet trial systems can be a major contributor to reducing development cycle time. Yet, to date there is little evidence available that they can do so. In the case of most systems, success has been difficult to demonstrate. When it is possible, it is often outside of the larger corporate mainstream with

smaller, focused service providers bringing a combination of experience and technology to bear. Why might this be?

PEOPLE, PROCESS AND TECHNOLOGY

In reality, electronics is the easy part. Successful clinical development depends on many aspects. The lack of success of electronics alone is due to a failure to understand that multiple complimentary pieces must be aligned. There are several examples of companies adopting an EDC solution, which is tacked onto the current clinical development and data management process, and more often than not is operated by staff with little incentive to make the system work to its full advantage. Such companies may be disappointed when the results, in terms of reduced time spent in clinical trials, do not accrue to the organisation, especially when the systems are expensive to buy and maintain. This can lead to the 'eternal pilot', where several such systems are brought in-house one after another, the change driven by disappointment or a desire to add just one more layer of functionality that a competitor system now provides.

The success of Internet clinical trials has never depended solely on technology, but rather on an organisation's ability to maximise its use – to align its staff and entire environment to the opportunities that technology provides. The ability to integrate people and process with technology demands an operating structure based on the following fundamental tenets: drug development; knowledge; project management expertise; and technology.

There is a need to employ project management staff experienced not only in the formal clinical trial process itself, but also in using technology solutions to apply their knowledge. These people need to possess skills different from those traditionally sought out in the pharmaceutical industry. The most fundamental changes brought about by electronic systems are that information is greater, flows much faster, and needs to be managed more efficiently. The focal point is making better decisions at an earlier stage, based on the earlier availability of information in greater quantities and of better quality. Clinical development requires many decisions, and an environment is therefore needed that encourages decisions to be made more quickly.

Project management thus requires:

- Relationship building and thought leadership to encourage understanding and communication about the need for change at all levels of company interaction
- Planning and organisational skills that are flexible and responsive enough to meet the challenges of rapid information flow within the clinical trial process
- Excellent teamwork skills to capture and utilise the opportunity for teambuilding and communication which electronic systems facilitate

Such people will no longer consider simply meeting project objectives to be an incentive. Instead, their performance will be measured by their ability to meet those objectives by fully utilising and even contributing to the expansion of technology capabilities. In my own company, we deliberately site our software development staff alongside project management staff in order to encourage day-to-day dialogue on tactical and strategic issues that affect the integration of the clinical trial process with the technology. This allows changes to be made rapidly in response to feedback from the field, as well as allowing capacity demands to be managed flexibly as nothing comes as a surprise.

Secondly, the technology needs to reflect drug development experience – that instinctive feel for

Web-based Query System Delivers Real-Time Data Validation

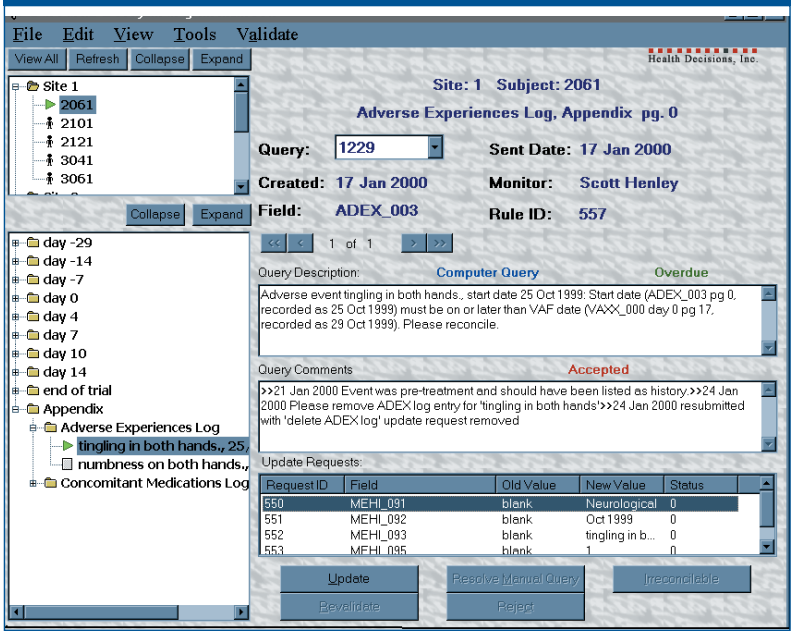

Table 1: Advantages of Integrated Trials Management Systems

- Better study tracking
  - Patient recruitment
  - Site performance
  - Adverse events
  - Drug supply
  - Site payment
- Real-time quality monitoring
- Reduced site monitoring
- Reduced data query resolution time
- Real-time monitoring of points of interest – for example liver function tests and adverse events
- Quicker, better decisions based on rapid data and information flow

how to get a new pharmaceutical product from discovery to the market. This instinct is traditionally possessed by individuals, but with the advent of new and better technologies that allow capture and retention of knowledge within organisations, there is every reason to believe that 'corporate' instinct will improve and become a more important contributor to the mix in the future. In many organisations, a gap remains in communication between those people with development knowledge and expertise and those who are designing and implementing the clinical trials software. Electronic systems can enormously improve communications and sharing of information – the basis on which decisions are made.

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Finally, there is the development process itself. Few pharmaceutical organisations of significant size fully comprehend the profound impact that rapid information flow will – and indeed already has – on its organisational processes. At the individual level, there will be less time available to dwell on tasks and activities, and I believe the opportunity presented by rapid information flow will increase the intensity of the average working day. This in itself has implications for the management of staff. At the project team level, decisions need to be made quicker and available information should be better taken advantage of, allowing more accurate decisions based less on opinion and judgement and more on hard facts in the form of incoming data.

Perhaps most important will be the strategic development decisions made at corporate level. We are already being presented with the data much earlier and this increases the quality of go or no-go decisions on products under development. At present, the pharmaceutical industry process has shifted only slightly and there are still far too many instances of technology delivering information rapidly, but the decision made being based upon that information taking weeks if not months. We are moving away from the days of the product 'champion' beating their fist upon the table and insisting their product deserves more time and financial backing. We can now design into our development programmes much higher quality, objective pivotal decision criteria, and can trust the information flow from electronic trials to deliver us data for those decisions more rapidly.

We must also understand the limitations of technology. Some major causes of delays in clinical trials are due to difficulty in accessing patients and the time taken to gain ethics approval and clinical drug supply. Technology may alert you more quickly to potential problems but it does not make them go away. Again, it is the combination of project management expertise and drug development know-how leveraged through technology that allows predicting, detecting and managing such predictable difficulties that translate into the greatest success.

MAINTAINING FLEXIBILITY

There will never be a single solution for delivering electronic trials. Integration of technology and software, perhaps even the emergence of common standards, is occurring as this is written. However, every clinical development programme differs in its detail. A good example is the ability of investigational sites to interact with whatever electronic trial solution the company decides to operate. We still find – and probably will do so for many years to come – that even though many investigators claim web connectivity, this is often a desktop computer down the corridor used by many others to access the Internet across a standard modem. It is for such an investigator that different ways of delivering an electronic solution must be found. Add to this the perceived risk of adopting one particular system over another, or indeed the need to have the skills and expertise to use several systems across different clinical trials, and true connectivity of the global research community is a long way off. We find that sites respond well to the choice of using full electronic data capture or optical mark read forms and can incorporate both in the same study. As the trial progresses and familiarity ensues, sites have the option of switching from paper to electronic data collection.

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CONCLUSION

New electronic clinical trial capabilities are recognised as providing the technology solution to many of the problems we have faced in reducing the time and cost of clinical development. There is every reason to expect that bottom line results will show just how effective these systems have become, but only if we recognise the need to integrate the technology with a new clinical trial and decision-making process which includes those people ready and motivated to take full advantage of the opportunity. In the rush to develop and implement the technology we must, above all, remember that, impressive as these tools are, they remain merely tools and it is ultimately the users who will determine how successful they are. We must not repeat the mistake of viewing technology in a narrow framework, simply speeding up existing processes. Technology does not so much speed up the clinical development process as redefine it.

Although data collection systems represent a clear step forward in clinical development capabilities, it is important to realise that the end point of this step is to speed up the clinical development process. Doing so also requires additional technology, in the form of a system that integrates data collection with data and query management, and processing information for review by the team. The end point of technology should be to allow rapid dissemination of incoming data that is a prerequisite for faster, earlier decisions about trial management as well as clinical development plans. This in turn leads to the realisation that in addition to technology, two critical components are useful in such systems to permit quicker, more effective management of studies and programmes as well as to allow sharing of drug development expertise. ◆

(1) Rosenberg, M, Bowden, M, (1998) Accelerating Drug Development with an Integrated Electronic Approach, *Eur Pharm Contr* August, pp56-64

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