Moving Towards an Electronic Environment

Michael Smyth at TransPerfect looks to the future of the paperless global trial – a necessity for companies looking to compete in the clinical development marketplace

With each passing year, clinical trials are becoming increasingly global. The business of product development is moving away from the traditional model in which studies are conducted primarily in the US – in fact, recent estimates indicate that within the next three years, up to 65 per cent of studies under FDA regulation will be conducted outside the US (1). A review of a US government clinical trials registry and of 300 published reports in major medical journals revealed that one third (157 of 509) of Phase III trials were being conducted entirely outside the US, with over half the study sites (13,521 of 24,206) used in these trials located overseas, many in eastern Europe and Asia (2).

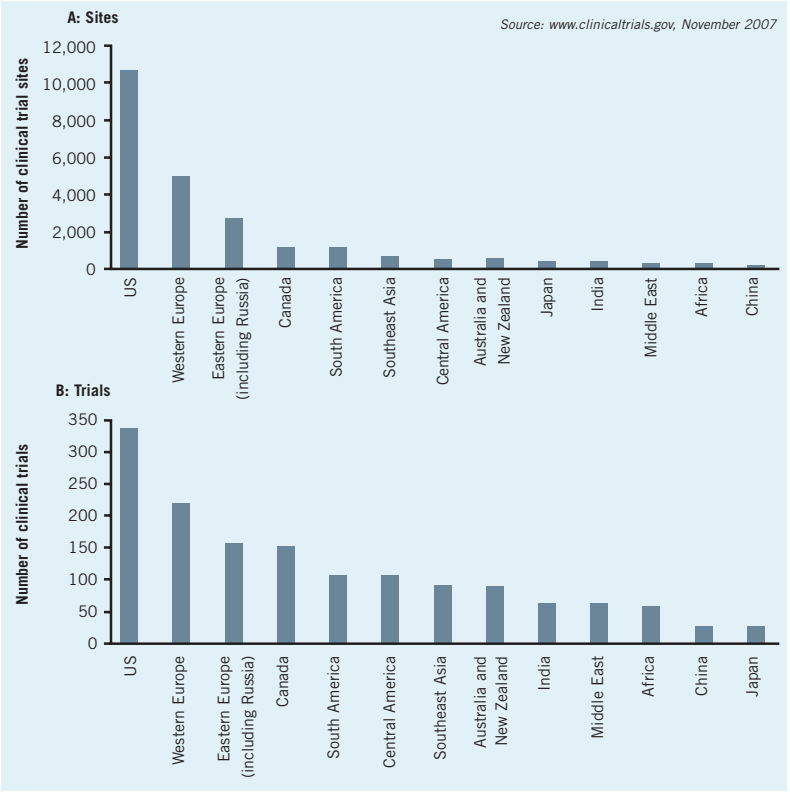
In a proactive move to take advantage of lower costs and treatment-naïve populations, many biopharmaceutical companies are looking beyond western Europe, with the expectation that the proportion of investigators will continue to shift in the direction of emerging African, Latin American and Asia Pacific 'hot spot' regions. Recent reports reveal that 8.5 per cent of active FDA-regulated investigators are based in central and eastern Europe, with Latin America and Asia following closely behind at 5.5 per cent each (3). In the coming years, additional markets will continue to emerge, thanks largely to the growing number of GCP-trained investigative sites in developing markets.

This globalising trend, coupled with biopharmaceutical companies' narrowing concentration to core competencies, has resulted in more outsourcing activity to the CRO market. The percentage of outsourced research and development expenditures has grown from 21.7 per cent in 2006 to a projected 28.3 per cent by 2010 (4). Meanwhile, the number of start-up biopharmaceutical companies continues to grow – largely due to increased investment funding and the lack of solid development pipelines in many of the larger companies – and it is expected that most of these startups will outsource all development activities.

Regardless of whether sponsors choose full-service or 'best in class' CROs or other providers, the strategic adoption of process-streamlining technologies is imperative to the success of global clinical trials. Electronic data collection (EDC) is the most prolific and accepted technology in the life sciences industry, yet the percentage of trials using EDC is only estimated to be in the range of 30 to 40 per cent. This is surprisingly low given the cost and time savings that EDC collection delivers. Estimates of cost savings realised by moving from paper to EDC range from $20 million (for a Phase II, 20-site, 12-month trial enrolling 200 patients) to over $60 million (for a Phase III, 24-month trial enrolling 2,000 patients) (5). Reasons cited for the lack of wider EDC adoption include a familiarity with paper workflows, lack of high-speed internet, and poor experiences with early EDC systems, among others.

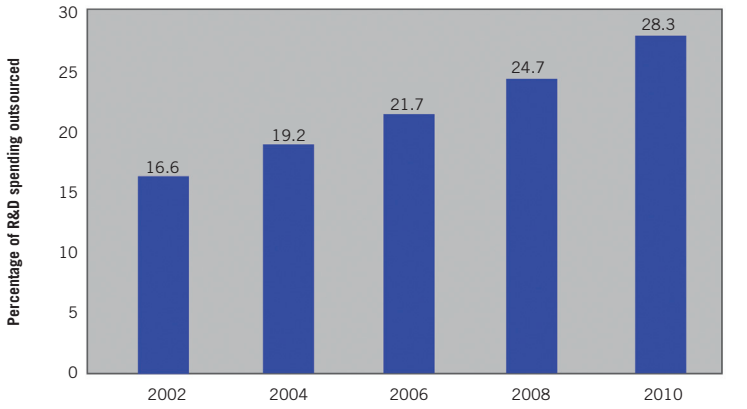
Figure 1: Open Phase III clinical trials sponsored by the 20 largest US-based pharmaceutical companies, November 2007

The size of the pharmaceutical companies is based on total annual healthcare revenue. The number of clinical trial sites (A) includes each location where a study is recruiting patients. The number of clinical trials (B) includes any trial conducted in a country that has at least one site (8).



Even though EDC is the technology most widely known and used by clinical development professionals, there are other available technologies which can offer study teams, CROs, and other vendor personnel the ability to further streamline clinical trials while increasing transparency to all study stakeholders. Tools like collaborative workspaces and electronic consent solutions can take the front end of a clinical trial into a paperless environment, complementing trial workflows that already include EDC.

Figure 2: Outsourcing expenditure



Source: Reuters Business Insight, 2003

RESISTANCE TO CHANGE

Given that many biopharmaceutical and medical device companies, as well as CROs, are loyal to their existing processes and standard operating procedures (SOPs), they will often default to executing their trials as they did 15 to 20 years ago. This includes maintaining paper trial master files (TMFs) and case report forms (CRFs), which, along with other study documents, must now be distributed to increasingly dispersed global sites using costly and time-consuming express mail.

It is impossible to identify precisely the reason – or set of reasons – for the persistence of these archaic processes, but there are plenty of possible candidates. Companies involved in the development of new therapies, particularly larger organisations, tend to be highly conservative in nature. The departments responsible for conducting clinical development worry about the risks of trying something new and often cite the FDA, EMEA, or other regulatory authority as the reason why it pays to stick to what they have always done. Others will blame their quality assurance (QA) departments, claiming that a new process would violate their SOPs.

CROs operate in much the same way as sponsors, and typically, the larger the CRO, the more resistance there is to 'outside the box' solutions, even in the face of clear evidence that they can operate more innovatively and efficiently. However, on the whole, CROs are perhaps less accountable, as they must often construct their practices around demands made by their biopharmaceutical clients (and the QA departments that audit them) in order to compete for and win business.

There is no question that 'turning the ship around' can be difficult for many companies, and there are usually growing pains associated with the process. Although senior management may often be held responsible for this resistance to change, many mid-level professionals are also partially at fault for not pushing innovative ideas – ideas that could reduce the need to hire more staff or allow current staff to work on multiple development programmes by creating increased operational efficiencies.

The biopharmaceutical industry is still working to find its footing on the best path forward, and while this happens, many professionals in the industry continue to get downsized out of jobs due to low profit margins at public companies, company mergers or acquisitions, or the failure of products in the pipeline. This uncertainty is further motivation to make wholesale changes to an approach that, by some accounts, could be considered broken.

THE FUTURE OF THE BIOPHARMACEUTICAL INDUSTRY

Companies outside the biopharmaceutical industry have traditionally been much quicker to adopt new technologies, including tools that allow employees to work remotely, enable 'just-in-time' shipping and delivery of packages, and cut paper burdens by creating a reliable and secure paperless world. While lagging behind is certainly no testament to the biopharmaceutical companies, the silver lining of this reluctance is that it is now possible to point to other industries' technology-related successes as pilot case studies exemplifying the close relationship between technology and efficiency.

Overcoming resistance to change is a process that requires an especially strong push to surmount the inertia of stagnation. One thing that is becoming clearer is that many of the common reasons for maintaining the status quo are changing. Placing blame on the FDA or EMEA is no longer a valid excuse, since the FDA now recommends electronic submissions via the Electronic Submissions Gateway. Various company personnel have commented that the FDA would not, for example, allow an investigator to sign a 1572 electronically, even though an investigator is permitted to sign patient documentation electronically in an EDC solution. This complaint is without merit, as the FDA publicly states, "The FDA will not check the signature on an electronic or paper-based submission unless there is a directed inspection involving that submission" (6). The EMEA is also moving towards electronic submissions, with recent revelations that Product Information Management (PIM) submissions will be "strongly recommended" by the third quarter of 2010 (7). This information runs contrary to what many industry professionals assume about agency

acceptance of electronic data; in fact, it means that companies who build their operational processes around working in an electronic environment have a clear competitive advantage over those using more traditional methods.

In order to prepare effectively for working in an electronic environment, large and mid-sized biopharmaceutical companies that operate in a brick-and-mortar environment should consider looking to small biopharmaceutical startups (some of whom they may already be tracking for partnership or acquisition). Because of monetary restraints, these companies are frequently forced to work virtually, and the operational efficiencies provided by technology are more than simply an advantage – they are a requirement in order to remain profitable. These companies understand the need to execute later phase studies at a lower cost, and are implementing a variety of technologies aimed at streamlining each clinical trial.

TECHNOLOGY SOLUTIONS: A REAL-WORLD LOOK

Based on an assessment of the technology solutions that are currently being used within the industry, below is a list of some of the tools and processes that have been implemented with positive outcomes. While this list does not include every single available technology solution, some of the more innovative ones are highlighted as they have the broadest impact on streamlining global clinical trials.

Collaboration Solutions

Collaboration is a popular buzzword in the clinical trials world, though too often it is no more than that: a word. In truth, most communication still happens via mailing or scanning paper documents, including project team meeting minutes, monitoring trip reports, and so on. In his article in the December 2009 edition of *The Monitor*, David Levin highlights his vision of a futuristic CRO that operates with "technology-optimised processes to improve trial performance, visibility and coordination among all stakeholders." Levin's vision of "collaboration" is a worthy goal, though to the industry's collective detriment, it languishes as a mere fantasy for the time being.

The industry standard remains a hierarchical arrangement with the sponsor at the top, the CRO reporting to the sponsor, the niche vendors reporting either directly to the sponsor or to the CRO, and at the bottom, the investigative sites participating in the particular trial. Sponsors often feel that communicating with investigative site personnel as they work to get buy-in on the study and protocol design, eCRF layout, and so on, represents sufficient collaboration between the top and bottom of the hierarchy. Sponsors typically see managing the CRO as their primary responsibility, and they leave direct vendor and site management almost entirely up to the CRO. As a result, tracking, reporting and communication among trial stakeholders most frequently occurs on a one-to-one basis at company level, rather than in a truly collaborative environment.

Web-based collaboration solutions can, and more importantly, *should* be changing the paradigm, even if only for the cost and time savings these systems offer. For global clinical trials, advanced systems also provide the helpful added benefit of a multilingual user interface that allows globally dispersed users to navigate the workspace in their native languages. These solutions can be used to operate in a paperless environment, securely distributing essential documents to investigative sites and offering electronic signature options to yield a paperless study start-up process.

As with the adoption of any new system, security is an important concern, so any collaborative technology solution must be 21 CFR Part 11 compliant. For instance, in a truly secure collaboration technology, regulatory binders can be compiled, viewed and searched electronically by only those users who have been set up to access that regulatory binder. Furthermore, as all data will ultimately need to be submitted in an eCTD format, TMFs should also be electronic, and your collaboration technology should allow you to limit access to TMFs to select groups of individuals within a sponsor company, extend access to CRO partners as necessary, and revoke access should you decide to switch CROs in the course of the study. Finally, look for a tool that offers detailed metrics and reporting options, which enable the sponsor, CRO and other stakeholders to monitor real-time user activity and even access reports through remote devices when travelling.

Regardless of which system best fits each company or clinical trial, the benefits of decreased costs and transparency across clinical trials will require company personnel to move outside of their paper-centric comfort zone. Mid-level managers

Table 1: Paper versus EDC cost comparison

	Phase II trial: 20 sites, 10 subjects per site, 12-month trial plus data cleaning		Phase II trial: 200 sites, 10 subjects per site, 24-month trial plus data cleaning	
	Paper	**Web EDC**	**Paper**	**Web EDC**
Total expenses	$732,000	$384,400	$11,436,000	$5,184,000
Operational savings from EDC		$347,600		$6,252,000
Shorter time to database lock (59 days)		$50,150,000		$18,290,000
Faster investigator recruiting (five days)		$1,550,000		$4,250,000
Operational savings plus accelerated product sales		$20,187,600		$60,652,000

Source: Forrester Research, 2004

should seek to identify and implement such collaborative systems for the operational efficiencies and – more importantly – the freed-up resources that can be redirected to bring products to market faster.

Electronic Consenting

Until recently, informed consent forms (ICFs) have always been delivered on paper, and have included information (presented at the reading level of a 13/14 year old) based on FDA regulations as well as comments from the Institutional Review Board (IRB) or Ethics Committee (EC) review process. But many biopharmaceutical companies also include additional language to reduce their liability risk, and as a result, ICFs have gradually grown in length to the point that, these days, it is not uncommon for them to reach 20 pages. This substantial length requires subject and study personnel to take an inordinate amount of time to properly review the ICF.

Electronic consenting provides subjects with the ability to review the ICF at their own speed and reading level and in their own language. They can click hyperlinks for clarification on terminology or even hear a section of the ICF read aloud in the language of their choice. In addition, each subject's questions, as well as the time he/she spends on each page, can be tracked, giving study administrators the confidence that forms are being carefully read and thoroughly understood.

Furthermore, these systems allow electronic consent to serve as the first notification to the sponsor or CRO that a subject is becoming a study participant. Integration with EDC systems can provide a full picture of the subject from time of consent up through study completion, as well as the ability to sort data on a visit-by-visit basis.

With the recent growth in the number of global trials, additional geographic complexities have entered into the equation, and these highlight another advantage of handling the consenting process electronically. Traditionally, subjects would read the paper ICF, review it with investigative site personnel and, finally, sign and date the document. However, when investigative sites are located all over the world, this method makes it virtually impossible to ensure that the consenting process is conducted uniformly study-wide. That's why an electronic solution that centralises and harmonises the consenting process across geographically diverse investigative sites will soon be the accepted standard for clinical trials, in much the same way as centralised laboratory analysis and centralised rating for CNS trials are now considered standard practices.

Finally, electronic consent solutions also provide valuable risk mitigation assistance for study sponsors. All too often, sponsors are saddled with significant legal bills or fines from lawsuits and actions imposed by regulatory agencies due to inadequacies in the consenting process. The FDA is one agency taking this problem very seriously, and they are currently drafting new Guidance for Industry on electronic consent solutions. This new Guidance will state that these solutions do a better job of educating potential subjects of the risks and benefits of participating in the clinical development process.

About the author

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CONCLUSION

It is clear that in order to remain competitive, biopharmaceutical companies and CROs will need to move much more quickly in adopting electronic solutions. While it may require minor modifications to existing SOPs and workflows, this adoption is ultimately in the best interests of these companies in order to maximise efficiencies in global clinical trials and development. Since moving to a fully paperless clinical trial is a major goal of the FDA, EMEA, and all major regulatory authorities, so too should it be the aspiration of any companies involved in submission of data to these bodies. Failure by any biopharmaceutical companies or CROs to move towards an electronic environment will leave them lagging behind those that do, crippling their ability to compete in the clinical development marketplace.

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