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The Internet in clinical trials: breaking the bottleneck?

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At a recent conference, *Clinical Trials: The Next Phase!* (London, UK, 13–14 December, 2000, organized by Access Conferences International), the use of the Internet in clinical trials, both to provide a global database of high quality clinical trial data and to aid patient recruitment, was debated. The clinical trial stage of drug development is the major bottleneck that prolongs the time between drug discovery and marketing, a fact made worse by an increase in the number of therapeutic targets from the mapping of the human genome, HTS and the advent of combinatorial chemistry. This is resulting in a requirement for larger, more complex trials, to which the access to patients, and investigation site performance cannot be matched.

Potential Internet strategies

C. David Hardison (First Consulting Group, Winston-Salem, NC, USA) started the conference by discussing the current problems of clinical trials in R&D, namely: poor success rate (1 in 5000 NCEs), time taken for drugs to reach the market (8–12 years), finite patent life, costs, and length of FDA submission (>500,000 pages; 0.5–5 years).

With an increasing number of websites being set up in the healthcare arena as online healthcentres, pharmacies and medical databases (e.g. http://www.netdoktor.com,http://www.allcures.com, http://healthwatch.medscape.com), is it possible to apply similar strategies to clinical trials?

The use of the Internet has increased significantly among physicians and by patients finding out more about their illness, potential treatments and support groups. Physicians are already using intranet strategies for medical records and prescriptions, which in itself could provide a basis for interactions between healthcare and clinical trials online. However, large amounts of time and money have been invested into current clinical trial systems, and clinical trial sites might be reluctant to embrace this new technology.

Hardison discussed the stages of e-business maturity, which are:

- publish: to build web awareness by the posting of healthcare and clinical trial information relevant to both patients and physicians;
- interact: encourage chatrooms, personalized information and healthcare communities online to engage the physician and patient;
- transact: incorporate online transactions including randomization, trial data capture, adverse-event reporting;
- integrate: combine data input with the generation of personal health records, trial database management; and
- transform: integration of all web interactions to form an end-to-end system between patients and physicians/trial sites, such that trial participation is a treatment option for all patients.

Hardison gave examples of research institutes that are already using Internet clinical trials in cancer care, namely the National Cancer Institute (Bethesda, MD, USA) and the M.D. Anderson Cancer Center (Houston, TX, USA), and the web-enabled International Verapamil/Trandolapril Study (INVEST; http://invest.biostat.ufl.edu) currently being run by the University of Florida Health Science Center (Gainesville, FL, USA). He continued by highlighting the advantages of a web-enabled trial system, including:

- online enrolment statistics;
- daily patient status reports;
- records of study visit activities;
- standardized letters, invoices, labels merged with patient database;
- automated calendar and resource management; resulting in
- annual cost savings of US$240,000 per site and increased revenue.

Hardison concluded by speculating that investigation sites will start using e-clinical trials to achieve:

- state-of-the-art drug therapies combined with a high level of healthcare for patients;

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- publication of clinical research in peer-reviewed journals;
- increased revenue and profitability;
- increased patient and physician recruitment; and
- increased visibility to sponsors.

To do this, Hardison emphasized the need for organizations to develop their own e-clinical strategy to ensure successful trial management.

Going global

Kathleen Drennan (Drennan Healthcare International, Chicago, IL, USA) discussed the requirement for global clinical trials and the role of the Internet in patient recruitment. She began by emphasizing that everyone who uses clinical trial websites must be able to trust that the sites adhere to the most stringent ethical regulations and that the information is of the highest credible standard.

So why go global? The greatest delay in clinical trials is in patient recruitment and, according to Centerwatch (Boston, MA, USA; http://www.centerwatch.com), 80% of trials fail to enrol the contracted number of patients. With the advent of genomics and combinatorial chemistry, and the need for pharmaceutical companies to increase their output of NCEs, clinical trials are set to get larger and more complex, particularly as science leads to personalized medicines. Drennan predicts that this will provide a great challenge to the existing systems of clinical trials, which have not been updated for several decades. She summarized the reasoning for global trials:

- increased number of NCEs required by pharmaceutical company growth;
- insufficiently qualified and experienced clinical investigators to manage large, complex trials;
- loss of patients that are treatment-naïve;
- differences in site costs;
- increase in the number of clinical trials, subjects and procedures required per NDA; and
- reduced paperwork required per trial in Europe, compared with the USA.

Drennan continued to discuss several issues that are crucial to the success of global Internet trials. In the US, for example, patients are often prevented from entering clinical trials by their healthcare providers, and so global patient recruitment would have to account for differences in how healthcare is paid for. There will be significant differences in regulatory guidelines for trials throughout the world. and limitations on methods of recruitment and advertising because of customs, language and advertising regulations. Moreover, there is likely to be variation in prevalence and type of disease, education and training of investigators, health-awareness of patients and the provision of the Internet technology required. These differences will not just apply to countries, but to regions within those countries.

A major risk concerning global trials is the potential for unethical drug development, for example, using third-world patients in trials for AIDS therapies, which might only then be used in the Western world. Drennan highlighted the need for harmonization of regulatory standards between countries, such as informed consent and information disclosure guidelines, drug approval regulations, NDA application processes, labeling, use of foreign data, and public health policy restrictions, to aid the introduction of new products into global regions. She also emphasized that one of the most important questions in global recruitment via the Internet is whether investigators are misleading patients, in that they can participate in clinical trials online, while maintaining the security and privacy of their medical records. Drennan concluded by identifying matters to be addressed before the clinical trial industry can take on Internet technology:

- How will division of labour and investigators' jobs change?
- Will industry pay for the upgrade in technology?
- How will small, unaffiliated sites keep up?
- Will there be an alliance rather than a competition between pharmaceutical companies?
- Will there be a lag-phase between integration of the technology and benefit to users?
- Can the Internet replace the skills and experience that benefit researchers in clinical trials?

Turning promise into practice

The keynote lecture of the conference was presented by Mike Conlon (University of Florida Health Science Center), who discussed his experience of the large, international web-based clinical trial, INVEST. INVEST is an online, randomized, open-label, post-market study of calcium antagonist versus beta-blocker treatment of hypertension in patients with coronary artery disease, which was designed in 1996 and comprises 869 sites in 15 countries with 22,467 enrolled patients.

The trial utilizes patented browser-based technology that provides a central database with worldwide real-time access. This technology manages all aspects of the trial, including recruitment, eligibility, randomization, online dispensing, and online information for trial-enrolled patients, sponsors and directors. The website is primarily used to recruit physicians rather than patients, but lessons for patient recruitment online can be learned from the strategies employed.

Conlon discussed the development and maintenance of the website. The aim was to simplify processes, reduce monitoring and use better tools for real-time online participation. Investigation sites either use an Internet connection and associated hardware provided by INVEST or provide their own. Physicians are trained online before they can recruit subjects and all recruitment forms, training manuals and documents are kept online. The eligibility of patients is determined in real-time online, and records of screened and eligible patients are

recorded automatically. In addition, randomization of eligible patients is automatic, and is linked to dispensing, which in some areas involves automated faxing of prescriptions to the pharmacy.

One major advantage of determining eligibility online and in real-time is that data can be validated while the patient is still present. Furthermore, reports of adverse events can be coded and followed up immediately, and sponsors and monitors informed automatically by e-mail. The database also suggests future visit dates, provides summaries of visits and encourages clean and complete data because fields cannot be left empty. This means that monitoring is carried out online and monitor visits might be reduced by 80%.

A significant issue concerning any e-clinical strategy is security of online patient data, and Conlon pointed out that with the security measures available for online processes, data kept on the Internet might actually be more secure than those kept on paper and transmitted by fax. Furthermore, Conlon emphasized that patients enrolled in INVEST have been informed of their participation in a web-based trial, and that this has not been an issue for them. Indeed, Conlon says that many patients are enthusiastic about doing research that might speed up drug development.

Finally, Conlon reported that the reaction of investigators to the INVEST trial has been encouraging, and that they appreciate the simplicity of the system, and are willing and able to use it for other trials.

Other viewpoints

In addition to the presentations highlighted here, there were several interesting talks about the logistics of using Internet technology for clinical trials. Michael Tinkler (Datatrak International, Newbury, UK) discussed the advantages of EDC over the Internet; David Kill (Quintiles, Bracknell, UK) provided an explanation of Internet-based clinical trials; Chris Goldsmith (BT Ignite, UK) explained how community working has advantages over electronic data capture (EDC) and Bron Kisler (Nextphase International, Redwood City, CA, USA) discussed e-clinical process optimization and an industry case study of electronic versus paper data-capture.

Linking this further to drug development, Ronald Lorjin (Amgen Europe, Lucerne, Switzerland) warned against treating the Internet in clinical trials as a 'panacea for all your pains', that is, expecting the Internet to solve the problems caused by poor design and organizational deficiencies; Fabrizio Gianfrate (GlaxoWellcome, Verona, Italy) talked about implementing technology-based solutions to reduce time-to-market and Andy Smithers (Profiad, Reading, UK) discussed using the Internet to maximize the potential of a managed investigator-network and its impact on clinical trial timelines. The issue of online patient recruitment was further addressed by David Brocklebank (Quintiles, Bracknell, UK), Dan McDonald and David Heck (both at Centerwatch), and a panel discussion chaired by Kathleen Drennan, and was complemented by a presentation underlining the regulatory and legal issues surrounding online clinical trials and healthcare by Louise Fullwood (Pinsent Curtis, London, UK).

The future

The Internet undoubtedly has a future in clinical trials, but will not be a substitute for good trial design and management. Several hurdles exist, and organizations will need to formulate a competitive e-strategy, taking into consideration ethical working practices, legal and regulatory affairs, global variation and available technological and human resources, to effectively begin to break the bottleneck.

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