

Internet-Based Clinical Trials

David Kill

In the past, there have been some fairly extreme under-estimates of the inventiveness of mankind (Fig. 1) and the usefulness of some of its inventions (Figs. 2 & 3). The internet, on the other hand, has been almost universally hailed as one of the greatest of all inventions (Fig. 4). I believe it is important to recognise the internet as a means to an end (albeit a very powerful one), but not the answer to life, the universe and everything. It is already having an impact on the way we run clinical trials and we should be using it more.

It is generally agreed that the drug development process can be made much more efficient. Each day of delay in marketing a drug costs a pharmaceutical company in the region of \$1.2 million, so there is considerable pressure to speed things up.

The days when CRAs reviewed a few 10-page CRFs during monitoring visits, then took investigators out to lunch, have long gone and menus have been replaced by lengthy and detailed SOPs. The advent of Good Clinical Practice (and ultimately ICH-GCP) has resulted in an enormous increase in the quality of clinical trials, but also huge increases in the time and effort required to run the trials and manage the large volumes of data generated. In addition, research by Andersen Consulting¹ has indicated that companies will have to produce four to six New Drug Applications per year to maintain leading positions in the industry.

However, some companies seem to be much quicker and more effective at developing new drugs than others. Writing in the Drug Information Journal, Kenneth Getz and Annick DeBruin² identified five practices within pharmaceutical companies that reduce development time:


1. Global project planning
2. Realistic protocols
3. Closer and more proactive collaboration with regulatory authorities
4. Use of project and data management and communication technologies
5. Project team cohesion and empowerment

They pointed out that technological solutions may be used to enhance internal processes, including:

- Project team communication
- Project planning and management
- Statistical analyses
- NDA preparation
- Earlier cleaning of clinical data

However, a report by Friedman, Billings, Ramsey³ indicated that process changes and cross-functional improvements have had as much impact as they can. They have reduced the mean time for clinical development from 86.7 months in the period 1993-5 to 70.3 months in 1996-8. The authors suggested that only use of the internet can make the even more noteworthy improvements we need.

There are now over 350 million internet users worldwide, and this number is expected to almost triple within four years. Although there are obvious ways in which the internet could be used to aid communication between project team members and between the project team and site staff, most effort seems to have been devoted to developing for capturing study data electronically at the site. In fact, there are now in the region of 60 Electronic Data Capture (EDC) systems available. The implication is that the site is where the delays occur and, to an extent, this is true. However, there are many areas where the power of the internet to enhance communication and allow real time access to data can facilitate the development process.



"Everything that can be invented has been invented."

Commissioner of
the US Office of
Patents, 1899

Fig 1

Many companies, large and small, are involved in developing EDC and other internet-based tools for clinical research. One would assume that not all of these systems (and their originators) will survive. What will characterise the survivors?

It is essential to learn from experience. Lessons learned relate to the site, Internet Service Providers (ISPs), training and support. I shall highlight some key tips for success:

- It is critical to establish what hardware and software the site possesses, and to upgrade if necessary. Nothing is more off-putting than a slow-running application, so a high-speed microprocessor, with adequate RAM, is essential, along with a fast internet connection (via modem or, preferably, broadband or permanent connection).
- If the facility to enter data offline is required it may be better to provide a laptop with the software already loaded, rather than attempt to load the software on to the site PC. However, this is an expensive option and busy trial sites could end up with a laptop per trial! Online data entry via a browser allows the site PC to be used without additional software, but is less flexible.
- It is essential to thoroughly train site staff who are to use the EDC system. Training should include connecting to the internet (via modem or LAN), accessing the application, and good password practice. On this latter issue, sharing of passwords

should be strictly forbidden. Where offline working is possible, staff must know the export and import processes.

- The choice of Internet Service Provider, or ISP, is of great importance. Performance league tables are available for some countries, but change frequently. It is a good idea to use large and popular providers, but there can still be problems. Some providers have Points of Presence, or POPs, in several countries and sometimes a local ISP is used to get to the main ISP. It is important that the site is able to access the internet via a local 'phone call rather than an international one.
- Once up and running, the site needs support, which is usually provided by a helpdesk. This should be available 24 hours a day, seven days a week and should be staffed by people with technical and language skills. Service Level Agreements should be established relating to such things as query resolution and hardware replacement. It goes without saying that calls should be tracked to resolution.

Attention to such factors and refinement of the process in the light of experience leads to successful EDC.

MSc/Diploma in Clinical Research

The Institute in conjunction with
Liverpool John Moores University

Applications are now being considered for a three-year part-time course leading to a post-graduate diploma (120 credits) and MSc (180 credits).

Prior qualifications and experience are taken into account when considering applications for direct entrance to the Masters research element of the course. The University is a leader in the recognition of accredited Prior Learning/Accredited Prior Experiential Learning.

PGDip £4,495

Single Modules £749

MSc Direct £1,500

For further information call the Institute on
+44 (0) 1628 829900



CRF Printing Headaches Cured!

You need CRF work produced fast,
with 100% accuracy and no time lost so

Depend on Us

Four Point Printing has over fifteen years'
expertise in Protocols, Diary Cards,
and all CRF work

We commit to

- Fast turn-rounds to beat your deadlines
- Trouble free production, all in-house
- Digital and Offset printing, highest quality
- 100% Quality Assurance check
- Reduce your overall costs
- UK and Worldwide Distribution
- Excellent value and impeccable service

When you must be sure, count on

4 **QUALITY**
SERVICE
VALUE
SPEED

BPIF four point printing

www.fourpoint.co.uk

01932 561163

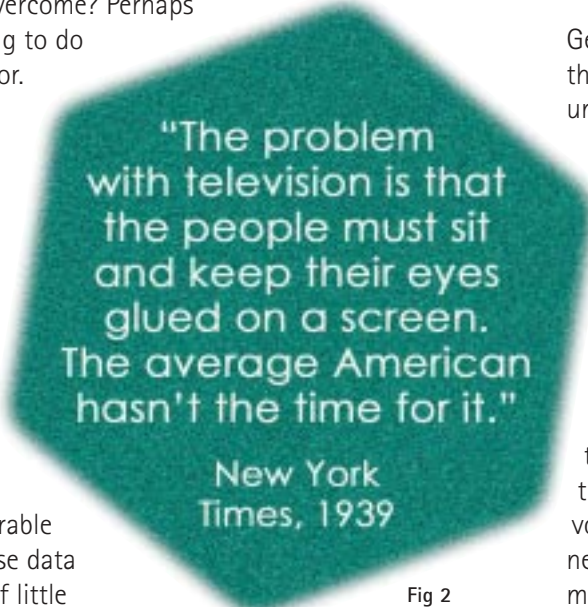
Beyond EDC...

There is now a great opportunity to go beyond EDC and re-think the entire clinical trial process, using the internet as the catalyst. What are the barriers we need to overcome? Perhaps

resistance is something to do with the comfort factor.

Everyone is familiar with paper and most people like it. It is tactile, smooth and pleasing to touch and acts like a security blanket. We can see it and know that it is there, containing our precious clinical trial data. The fact that we have to go to considerable trouble to extract those data and analyse them is of little account, or has been until quite

recently. There are also many myths and tales of internet use and problems with connection. In the end it is, of course, the safer option to allow someone else to pioneer electronic or eBusiness processes and learn from their mistakes.



"The problem with television is that the people must sit and keep their eyes glued on a screen. The average American hasn't the time for it."

New York Times, 1939

Fig 2

A useful starting point for a review of the use of the internet in clinical trials is to examine the drivers of eBusiness in the pharmaceutical industry.

Genomics, combinatorial chemistry and high throughput screening are generating unprecedented numbers of drug candidates for clinical development. In addition, many top tier pharmaceutical companies are now committed to launching three or more major New Chemical Entities per year, instead of the traditional one. These factors are straining development resources to, or beyond, their limit.

The average New Drug Application submitted to the FDA now includes data from 60 to 70 trials, including 4000-5000 patients. The volumes of data involved are enormous. The new wave of trials will require access to many more patients than are attainable by conventional means. Pharmaceutical companies and Contract Research Organisations are already conducting trials in Eastern Europe, South East Asia, India, China and Latin America, but even these sources may be insufficient if patients are recruited by conventional means. When they are



 **Pivotal Laboratories**
THE DEDICATED CLINICAL LABORATORY

NEED A CENTRAL LABORATORY?
One-Stop Shop or Best in Class?

At Pivotal Laboratories, we are focused entirely on providing excellence in central laboratory services for clinical trials.
And that's it - simple, really!

Spoil yourself...choose best in class.

Pivotal Laboratories.
Excellence in all areas of central laboratory support for clinical trials.

For further information, please contact:

Mr Steve McAteer Managing Director	Dr Alan Craig Non-Executive Chairman	Mr Peter Napier Head of Business Development
--	--	--

Pivotal Laboratories Ltd
Pivotal House
Aviator Court
Clifton Moorgate
York
YO30 4UT

Tel: +44 (0) 1904 699400
Fax: +44 (0) 1904 699401
e-mail: info@pivotal-labs.com
web: www.pivotal-labs.com

...excellence in clinical science

recruited, gathering, managing and processing the data by conventional means will be beyond the capacity of sites, pharmaceutical companies and CROs.

Sales and Marketing considerations also drive the adoption of new technologies in the pharmaceutical industry. Multiple products competing for a limited number of prescriptions has led companies to employ large numbers of sales representatives, who are finding it increasingly difficult to see prescribers, despite the use of increasingly sophisticated electronic territory management systems. Alternative means of reaching the physicians are therefore required. In the US, at least, regulations regarding direct-to-consumer promotion of medicines have been relaxed and advertisements for a number of products may be seen on TV. However, consumers, whether patients or not, are increasingly interested in becoming participants with their doctors in safeguarding their health and health-related websites are extremely popular. The related growth in prescribing over the internet may be less desirable.

Technology is also a driver, with new hardware and software constantly becoming available. I believe that we shall have to get used to more frequent upgrades and replacement of hardware and software than we are accustomed to. Standards are required in order that different systems are compatible with each other.

Steps to full eResearch

Implementing eBusiness processes within an organisation may take the form of a series of steps.

- The ground level is where many companies are now, using people in well-defined job roles that involve processing large quantities of paper. These processes may have been progressively refined to be as efficient as possible, so that maintaining the status quo can seem an attractive option. As they say: "If it ain't broke, don't fix it!" However, this approach could be commercially unwise, given the strategic factors discussed earlier.
- The first step in implementing eBusiness processes is to automate some existing functions, to relieve the burden on the people. Internal consolidation and integration of internal functions and selection of a small number of preferred external suppliers leads to cost savings. Use is made of email technology or an intranet to facilitate internal communication, while



SEE US IN
THE ICR ONLINE
SERVICES DIRECTORY

Take a fresh look at Browncroft Events

BRINGING THE PIECES TOGETHER

- investigator meetings
- conferences & exhibitions
- company meetings
- sales & marketing events
- training days

**Call Judi Reader
on +44 (0)1628 829966**

PROVIDERS OF EVENT MANAGEMENT SERVICES TO THE
PHARMACEUTICAL INDUSTRY FOR OVER 12 YEARS



Browncroft Events
3A Grove Park
White Waltham
Maidenhead
Berkshire
SL6 3LW UK

Print Management Solutions for Clinical Trials

- Large or small quantities
- Cost-effective solutions
- Document design, print and distribution
- Advice on finishing and binding

- CRFs
- Additional Pads
- QoL Questionnaires
- Manuals
- Diary Cards
- Patient Cards
- Event Form Booklets
- Follow-up Books

For a quick, free quotation please contact Melanie Kirk on **0161 495 4801** or click on www.pulsarhealthcare.com



Chetham House Bird Hall Lane
Cheshire Heath Cheshire SK3 0ZP
0161 495 4801 | 0161 495 4546

the internet is used to provide a point of contact or exchange for suppliers and customers.

- In step two, web-based EDC, project websites and web-based recruitment enter the equation. These lead to significant cost and resource savings and more rapid decision-making, but again impact only part of the clinical trial process.
- The final stage is one in which there are true inter-enterprise processes through common goals, streamlined processes across enterprises and corporate use of knowledge, resulting in a 'learning organisation' that is able to react rapidly and effectively to changes in its environment.

Companies that automate most of their internal processes effectively are able to turn their attention outwards, towards their customers, rather than focussing on internal processes.

The pharmaceutical industry spends less on IT than other industries. The advent of the internet will result in a significant increase in hardware and software expenditure, in the expectation of reduced costs in other areas. Compliance with regulatory requirements relating to electronic records and electronic signatures will be costly: indeed it has been estimated that companies may spend more than twice as much to comply with FDA 21 CFR Part 11 as they did to become Y2K compliant!⁴

The objectives of eBusiness in the pharmaceutical industry are to:

- Widen access to the clinical trial process for both physicians and patients
- Streamline and speed up the clinical trial process
- Educate physicians and patients on emerging products and therapies
- Speed up penetration of markets by new products
- Facilitate earlier and better decision-making by creating an information-rich environment

A large number of potential internet-based products may be envisioned that may be grouped together and accessed by the interested parties via portals. A portal is a website that allows access to authorised users, in these cases consumers (who may or may not be patients), physicians (who may or may not be investigators) and pharmaceutical company and CRO staff. Having accessed the portal, they may enter data, review documents, communicate with a project team, review payment status or

request a phone call, amongst other things. Access through each portal may be free or restricted, as appropriate.

Key ingredients

Key ingredients to success in developing internet-based products include:

- Finding the right partners;
- Making adequate human and financial resources available – dedicated teams and significant money are required
- Encouraging innovation
- Involving cross-enterprise participation

It is important to realise that becoming an eBusiness involves significant changes in working practices and attitudes, and sufficient management resource must be devoted to encouraging and managing the necessary shift in culture.

The internet offers connectivity between the players in the clinical research game. It and associated technologies can offer real-time access to study data and ad hoc querying of data warehouses, so that decision-making can be based on knowledge, not projections.

There are a number of clear requirements for web-based products for clinical development:

- They should make use of industry standards for data interchange, software, databases, etc. The Clinical Data Interchange Standards Consortium (CDISC), for example, is "an open, multidisciplinary, non-profit organization committed to the development of industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and biopharmaceutical product development."
- They should adhere to the highest practical security standards, as governed by regulatory or governmental requirements, including the regulations relating to electronic records and signatures (e.g. FDA 21 CFR Part 11) and data protection. At the same time, they should cater for practical user needs.
- When considering a system, stability of the IT components and of the suppliers of the components is critical. Partner companies should have financial strength and domain expertise.
- Applications should be operable for 2, 2000, or 20,000 users with no difference in performance and available globally and not just regionally.
- Helpline and support capabilities should

compact bench top centrifuges

CEP2000

If you are looking for bench top centrifuges for your clinical trial, Capricorn can supply the answer. For refrigerated and room temperature centrifuges contact David on 01425 480455 for an immediate response.



Room temperature & refrigerated bench top centrifuges

MIKRO 22R



Tel: +44 (0)1425 480455
Fax: +44 (0)1425 480366
www.capricorn-labs.co.uk
email david@capricorn-labs.co.uk



CAPRICORN
laboratory equipment

A clinical revolution

offer 24 by 7 hours availability, highly skilled, responsive staff and true multi-lingual capability, so that one call resolution will be a reality.

The re-thinking of the clinical trial process leads to a suite of integrated internet-based products, rather than a number of discrete modules.

It is important that we do not just web-enable our current processes, but re-think those processes in the light of available technologies. At the moment, electronic data entry screens often closely resemble paper forms, whereas technology could allow a format more suitable for the workflow of the Investigator, using portable devices with smaller screens.

EDC and patient recruitment are merely the first stage of the eClinical trial. It is possible to develop ways of presenting data relating to trial progress in real time that may be customised according to the needs of the reviewer. New

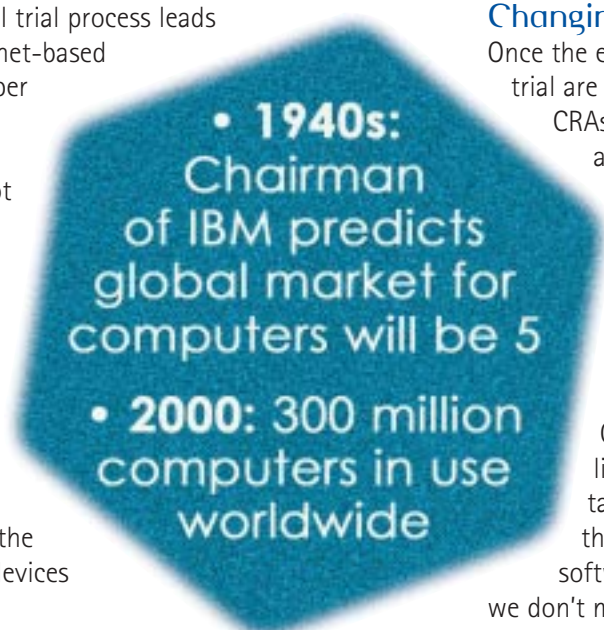


Fig 3

ways of gathering data from patients are in use or in development, for example via WAP-phones, GSM-enabled PDAs and monitoring devices that transmit data by radio to the internet.

Changing roles

Once the elements of the internet-based clinical trial are in place, how will the jobs of the CRAs and data management staff be affected? It is clear that it will be necessary to re-think processes, workflow and roles. There is no point in automating a bad process and so a fundamental re-think of the way we do things, taking account of the technologies available, should be the first step. Once systems are in place, we should listen to feedback from the users and take corrective action where necessary: their buy-in is critical to success. Many software vendors take the attitude that 'if we don't make it, you don't need it', and this is not acceptable: we, as customers, are entitled to expect products that are flexible enough to meet our changing needs.

The eClinical trial product portfolio will also cater for other interested parties, such as

Good Hope Hospital
 NHS Trust

ICH GCP
TRAINING PROGRAMME

Need to ensure your research complies with Research Governance?
Need to meet requirements of EU Directive 2001/20/EC?
An introduction to the 13 principles of ICH GCP and how they apply to carrying out research in an NHS Care Organisation.
Low cost, high quality training available - income generated will support researchers in the NHS.

Dates available throughout 2003

For further information please contact:
Emma Bouic, Research Office,
Good Hope Hospital NHS Trust
Tel: 0121 378 6206 ext 2580

emma.bouic@goodhot.wmids.nhs.uk

Reading someone else's copy
of Clinical Research focus?

This lively, informative and thought-provoking journal keeps all members of the Institute of Clinical Research in touch. We publish articles on topical issues and best practice, written by Institute members and other experts who interpret the news that affects us all from day to day.

Every member of the Institute benefits from:

- Eight issues of Clinical Research focus throughout the year, with a searchable index of back issues and PDF downloads via our website
- Essential reference publications
- Cost-effective educational workshops and courses, leading to a series of accredited academic qualifications in conjunction with Liverpool John Moores University
- A telephone helpline for information and advice
- Committees and forums to help make your voice heard
- Informal networking opportunities to share views and advice with other members throughout the industry

Becoming a member of the Institute only costs £45, and if you join now, your membership will run until the end of March 2003.

Simply complete the form on page 18 and send it back to us today.

Can you afford to keep missing out?

regulatory authorities and independent ethics committees. Although regulators are generally in favour of electronic submissions, the position is less clear with respect to independent ethics committees and the question of funding of hardware, software and internet access is likely to arise.

In conclusion, the internet-based clinical trial process is inevitable and requires standards, money, resources, innovation and a step-wise evolutionary approach. We should learn from internet applications such as EDC, as some greater opportunities lie just around the corner.

David Kill is Director, Contract Quality Assurance Services, Europe, PAREXEL International.

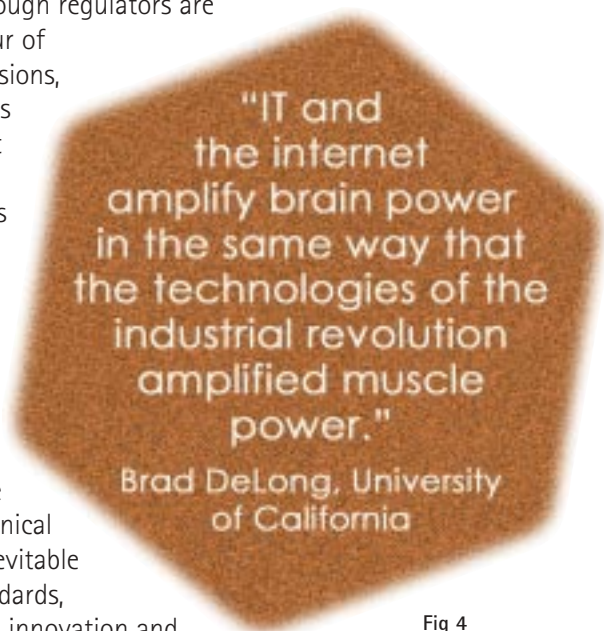


Fig 4

Acknowledgement

I would like to thank Dr Mark Goldberg, President, Perceptive Informatics Inc., for his helpful comments on this article.

References

- 1 Andersen Consulting (2000): "R&D and the internet. Opportunities to profit from web-enabled pharmaceutical research & development", Research report.
- 2 Getz, K.A. & DeBruin, A (2000): "Breaking the development speed barrier: Assessing successful practices of the fastest drug development companies", Drug Information Journal 34(3), p725-36.
- 3 Friedman, Billings, Ramsey & Co., Inc. (2000): "e-Pharma: Accelerating clinical trials and enhancing details", Research report.
- 4 Gambrell, S (2002): "The Unexpected Outcomes of 21 CFR Compliance", CenterWatch 9(6), 1-7.



Medi Lab

High Quality Contract Laboratory Services
Salford Quays, Manchester, England.

Safety First: -

Medi-Lab has 15 years experience in the provision of safety analysis and support for Phase I-IV Clinical Trial Studies.

P.K. Validation & Analysis: -

Expert method development, validation and analysis is available in our PK Laboratory which is equipped with an enviable range of GCMS, LCMS, HPLC etc. analysers.



For further information, quotations or to discuss preferred partnership arrangements, strategic alliances etc. please contact:

Brian Owen, Managing Director
Medi-Lab Ltd., Mumberry House, New Barn Lane
Leigh, Lancashire WN7 3UD, England

Telephone: +44(0) 1942 260414 Facsimile: +44(0) 1942 269180
e-mail: brian.owen@medi-lab.co.uk

