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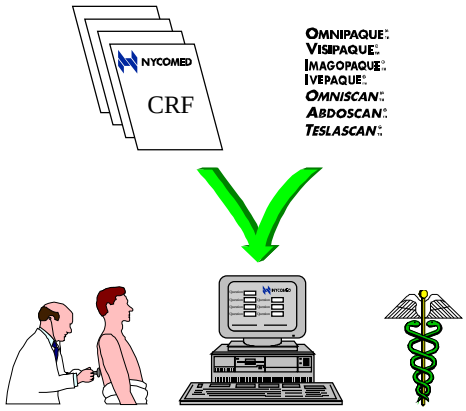
New Technology Systems Being Tried in the Collection of Clinical Trials Data in the Pharmaceutical Industry - A user centred comparison using HCI methods



A dissertation submitted in partial fulfilment of the requirements for the Open University's Master of Science Degree in Computing for Commerce and Industry

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Preface

This project is based on my belief that new technology projects should be an equal partnership between developer and user that can only be fruitful when built on mutual trust and earned respect. The systems development process to achieve this must be and be seen to be a collaborative and iterative process where the goal is to improve the quality of work life as suggested in Blomberg and Henderson (1990). Computers are an indispensable part of our daily working life and as such can affect our whole level of job performance and satisfaction. A choice of a system that the user subjectively perceives as poor or inappropriate can have far reaching effects for the employee and the business. Only with this in mind will systems developers increase the currently poor percentage of successful IT projects and businesses will begin to realise the benefits of using new technology. This view is shared by Donald Norman interviewed in Preece *et al.* (1994). He says there "The real challenge is to raise designers' sensitivities so that we can design things that people can use".

I work as an IT systems developer in a group of eight people amongst the users in the Clinical R&D department of a major pharmaceutical company. This role can be compared to that of an Ethnographer. Preece *et al.* (1994) describes Ethnography as the practice of researchers immersing themselves in the situation about which they want to learn. In an IT setting this means becoming as close to a user as possible to understand the real life tasks and problems faced in using a computer system in context. Where I work almost every activity requires the use of a computer. I have acted as a local helpdesk for three years filtering out problems that would otherwise have been handled by our central helpdesk and have also worked as a Clinical Data Manager (CDM). My knowledge of the clinical trial process and the pharmaceutical industry is gained first hand through this ethnographic interaction.

I would like to thank the staff of Clinical R&D especially the Clinical Data Managers who have been my guinea pigs and my inspiration with their positive feedback. The Clinical Data Systems department, especially my manager, who have allowed me and helped me to implement new systems based on my ideas and the Investigators that have been on the receiving end of my implementations. The systems implemented in the field have been implemented in live trials and not pilot studies and I am indebted to the project managers for allowing me to do this at an unknown but hopefully low risk to their projects.

Thanks to the Open University supervisors who have contributed their time and interest in giving critical and constructive criticism during the period of the research.

Finally thanks to my wife for all the cups of tea. Thank you Kirsten.

Contents

Tables and Figures

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ABSTRACT

The pharmaceutical industry is facing the challenge of increasing R&D costs due to more complex development and clinical testing, falling profits due to market pressures and increasing competition. This is resulting in a push to get products to the market faster and for resource savings. At the same time Nycomed and other pharmaceutical companies are using methods of collecting data for analysis of potential products that have changed little in the last decade. New technology is being tested for the collection of clinical trial data in an attempt to achieve three aims; 1) reduce trial duration, 2) improve the quality assurance process and 3) reduce resource use. Although new technology solutions have existed for more than ten years only a minority of trials use them. It is suggested that this is because of a failure to change the paper paradigm when implementing electronic data capture solutions and thereby not using computers effectively. A new paradigm is proposed based on the principles of Human-Computer Interaction (HCI) where carefully designed technologies are implemented into suitable environments for the collection of specific data types. Several prototype systems are created, each designed for a specific purpose in a specific environment and tested these in the true context in which they would be used. These contextual evaluations have shown that new technology can be applied successfully to the data capture process and result in faster collection with less errors, thus using less resources and providing a potential for reducing the trial duration. In addition to performance improvements the majority of users in the evaluations have judged the new technologies as ‘better’ than the current technologies used for the same tasks. These results show that systems developed in the new paradigm fulfil the aims of the project and that therefore the new paradigm is valid.

1. INTRODUCTION

1.1 The Project Domain

The project is set in the domain of Clinical R&D in the pharmaceutical industry where new medical products to be used for the diagnosis or treatment of patients in need of health care are tested prior to their approval for marketing. The company in which I am employed makes medical imaging contrast agents or contrast media as they are often called. These are agents introduced into the body to highlight specific problem areas when pictures of the body, known as images, are taken using such medical technologies as x-ray, Magnetic Resonance Imaging (MRI), Ultrasound and other newer methods.

Developing a marketable drug can take eight to twelve years and figures from Daniels (1996) suggest that it can cost up to $500m. Up to six years and 30% of development costs can be used in Clinical R&D according to figures given in McCollum (1997) and de Somer and Zipfel (1997). Sales revenues, however, justify this enormous effort. Scrip's Yearbook (1995), Daniels (1996) and de Somer and Zipfel (1997) state that leading drugs can gross over $1m per day on a world-wide basis.

The development of a new drug starts in the laboratory with the creation of a New Chemical Entity (NCE) with certain desired properties. To take it further a Sponsor is required willing to pay the substantial costs of continued development and testing. The Sponsor may be a large pharmaceutical company, as in the case of my employer, or other research organisation. The NCE, by now called a drug, passes through pre-clinical testing before finally coming into Clinical R&D to be tested on real patients. According to the Impact promotional material, Fraser Williams (1994), only one in 4,000 NCEs ever make it to the market and de Somer and Zipfel (1997) suggest that only one in three of those break even on the development costs.

Clinical testing is conducted in order to show that the new drug works, is safe and that it produces some benefit for the patient. To do this a number of research studies called clinical trials are conducted. The trials are conducted by doctors, termed Investigators in this context. As with any research study, data needs to be collected. The data is collected on forms called Case Report Forms (CRF). Once the active phase of the research is completed the collected data is statistically analysed and the results presented in the Clinical Trial Report. Several reports are grouped together into a document called 'The File'. This is sent to national drug regulatory authorities in order to seek permission to market the drug.

1.2 The Problem

Producing a new drug is costly, takes a long time and as de Somer and Zipfel (1997) emphasise, is becoming more complex due to more stringent regulations on new drug testing. Holzer and Honegger (1997), Payne (1998) and Vincenzi (1998) suggest the main problem facing the industry now is to reduce development times in the face of this increasing complexity.

In clinical trials the planning of the trial and the writing of the report are knowledge based tasks where technology could only play a limited role. The data collection task, however, is a labour intensive, highly repetitive process, which T833 (1995) suggests are the conditions making the implementation of new technology appropriate.

The data collection process and the resulting process of removing errors from the data are known to use a high amount of resource and to extend the trial duration. Until the last errors are removed from the database, the data cannot be analysed and the report cannot be written.

Figure 1.1 shows the data flow for the data collection process.

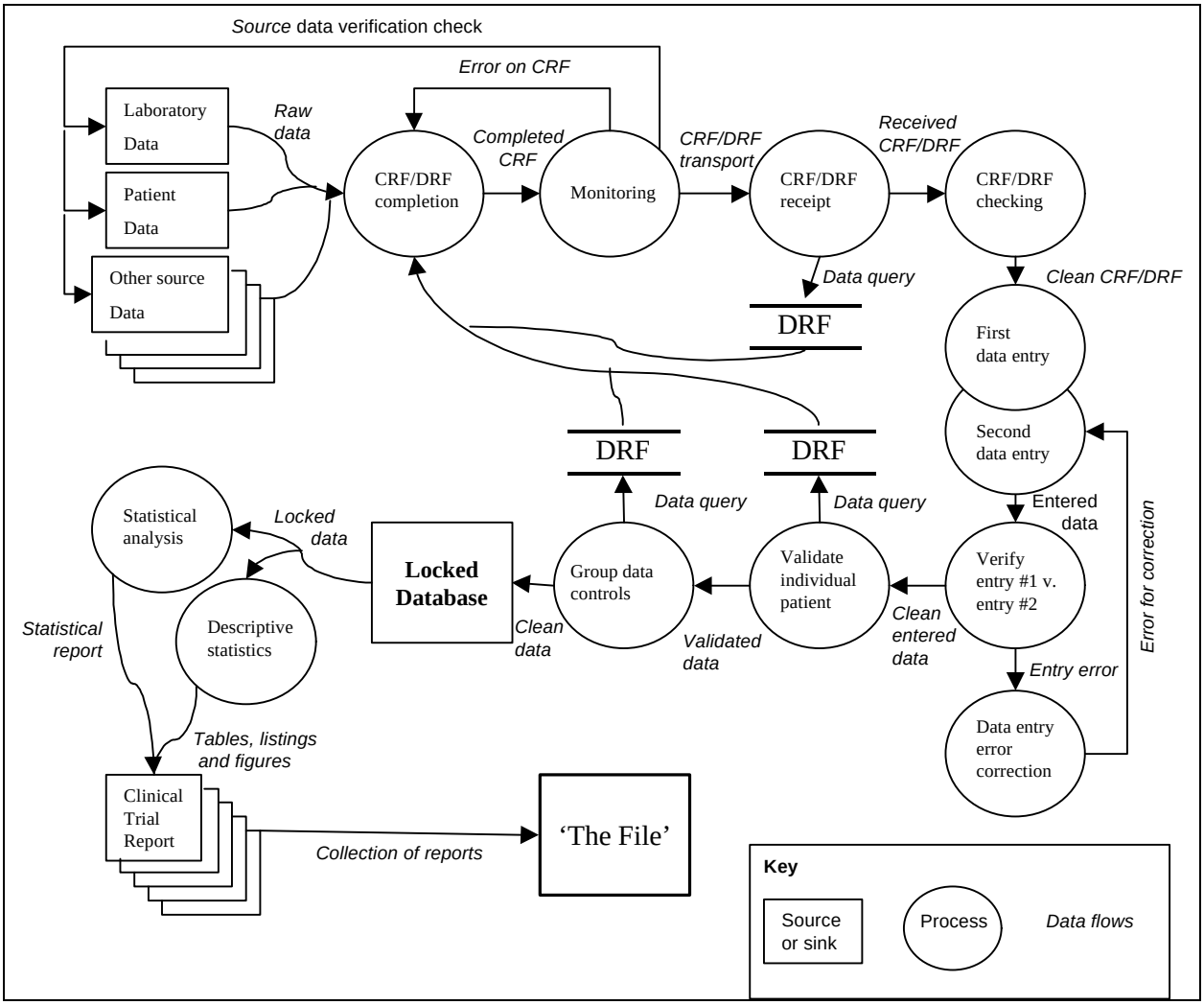

Figure 1.1, *Data flow diagram showing the data collection process*

The data starts as raw data from many sources. This data is then recorded onto the CRF. The CRFs are checked in a process called monitoring before being sent to the Sponsor where they are checked again and then entered into a database. Several more levels of quality assurance are performed: verification, validation and group data control. If errors are detected at any stage, a request for correction called a Data Request Form (DRF) is sent to the Investigator. Once all CRFs have been entered and all errors corrected the database is locked to prevent any more changes. The report can then be written and added to The File.

The computerisation of this data flow is the problem that is addressed in this project.

1.3 A Brief History of Past Research

Experimentation into new technology in data collection has been ongoing for more than 10 years according to Vogel (1997) and Konisky (1996). Lawton (1998) adds that this has been with varying degrees of success.

There are three commonly given aims by most authors, e.g. Vogel (1997), Galer (1998), Henderson (1997), Mirgoli (1996), Lawton (1998), for using new technology:

1. Reduce trial duration
2. Improve the quality assurance process
3. Save resources.

These three aims are interlinked. Errors resulting from a poor quality assurance process need to be removed and this uses resources. Errors generally take a long time to be corrected and this extends the duration of the trial. Lawton (1998) identifies a fourth aim and that is the reduction in paper usage. The American Food and Drug Administration (FDA) also have this as an aim according to Mitchard (1996).

Systems developed for the collection of clinical trial data are based on two different technologies. Electronic Data Capture (EDC), mainly in the form of Remote Data Entry (RDE) where a computer with an intelligent entry form, often called the electronic CRF or simply the eCRF is used. And, computer readable forms using Optical Mark Recognition (OMR) or Optical Character Recognition (OCR) using special forms which can be 'read' by computer. Papers giving an overview of electronic data capture include Konisky (1996), Nell (1996) and Callahan-Squire (1996). Papers giving an overview of data capture using OMR/OCR include Kampfner (1996), Blahunka (1996) and Abril and Fidora (1996).

Table 1.1 shows the results of a 1995 survey by Coopers and Lybrand (adapted from Carroll, 1996). Seventy eight pharmaceutical companies using or thinking of using these technologies in the data capture process were surveyed.

Table 1.1, *Summary of technology use and intentions*

Technology	PC		OCR		Pen	
No Experience	12	15%	22	28%	28	35%
Considering	16	21%	33	42%	27	35%
Tried and Tested *	24	31%	17	22%	21	27%
Regular Use	26	33%	6	8%	2	3%
Total	78		78		78	

* But not in regular use

It shows that PCs are the most used technology, OCR is next and pen technology is little used. From presentations at electronic data capture conferences the use of the word 'Regular' in this table could be questioned.

Table 1.1 shows a figure of 33% of companies using PC solutions. Pascal (1998) suggests that only 15% of all of a company's trials may be suitable for the application of RDE due to numbers of centres, size of CRFs, and other factors. These two figures combined suggest that only a

maximum of 5% of trials may currently be using PC based RDE systems. Vogel (1997) confirms this figure based on 1996 statistics.

This project will focus on the electronic data capture methods of data collection and not OMR/OCR. The main aim of applying new technology is to improve the quality assurance process. This improvement is most effective if errors are prevented at source rather than being removed after they have been introduced, a major point identified by W. Edwards Deming in Walton (1986) and in Schwörer (1997). OMR/OCR still uses paper for collecting the data and therefore it cannot affect the quality assurance process during data collection. OMR/OCR will reduce the time taken to transfer data from the CRF into the database and if data entry is a critical path activity then there is a potential to reduce trial duration.

1.4 Rationale for the Research

Table 1.2 shows a summary of reported reductions in the metric of last patient complete to database locked in comparative trials between traditional methods of data collection and remote data entry based systems. It can be seen that considerable reductions can be achieved.

Table 1.2, *Pilot study reductions in time from last patient to locked database*

Company	Time to locked database - conventional trial (days)	Time to locked database – RDE trial (days)
Zeneca [1)]		4 month savings
Zeneca [1)]	59	15
Undisclosed [1)]	90	2
Abbot Labs. [1)]	36	8
RSM [1)]	70	20
C&L [1), 2)]	300	14
Zeneca [3)]	80	18.5
ACT [3)]	Not given	14
ACT [3)]	Not given	1

1) Remote Data Capture Conferences Philadelphia ‘96 and London ‘96
2) Coopers and Lybrand typical figures from company consultancy (Carroll, 1996)
3) Robert Vogel in Applied Clinical Trials, Vol. 6, num. 5, May 1997 (Vogel, 1997)

There is a pressure to reduce trial duration. Table 1.2 shows that RDE can achieve this because the time to lock the database is on a trial’s critical path. Despite this only 5% of trials are currently employing it. There is clearly a need to investigate why so few trials are taking advantage of the possibilities.

There are several causes of unsuccessful new technology implementations. White (1997) suggests that failure to manage the complexities and Bennetts and Wood-Harper (1997) suggest badly managed expectations. Cost and time overrun and failure of the system to meet requirements, suggested by Lock (1992), PMT605 (1987) and T833 (1995) as reasons for an unsatisfactory project outcome, can be seen as consequences of failing to manage complexity and expectations. T833 (1995) highlights failure to change an existing paradigm as another reason for failure. These are the reasons for the failure of RDE systems in the pharmaceutical industry. Systems have been

too complex, trying to capture all data into one electronic form, and have had too high expectations placed upon them. The complexity in this case is not detail complexity. RDE systems are quite a simple concept. However, as Senge (1990) would describe it, there is a dynamic complexity because of all of the different environments, data types and users involved in collecting the data into one system.

This project suggests a new paradigm for electronic data capture based on Human-Computer Interaction (HCI) principles. The three main aims of applying new technology were given as; to reduce trial duration, improve the quality assurance process and save resources. In PMT607 (1990, Unit 1, p.39) these are listed indirectly as three of the main benefits of applying the HCI; improved productivity, fewer errors and reduced costs. Improved user satisfaction is also listed.

In PMT607 (1990, Unit 1, p.7) HCI is defined as "About understanding task, user and environmental factors in order to *design* systems that can be *used* effectively in the *context* [authors italics] in which they are placed". Shackel (1989) describes usability as the dynamic interplay between the system, task, user and environment. The new paradigm is therefore:

> *The use of computers for data collection using various techniques suited to each data type and environmental combination as opposed to the old paradigm of one eCRF for all data types and all environments. The aim of the paradigm shift is to reduce the dynamic complexity and allow better management of expectations for all users and other affected persons.*

It is important when introducing new technology that the human side of the change is not neglected. This requires that users be involved in the change process. The measurement of users' attitudes and preferences should be an integral part of any new technology project. The literature search found no reports of research into user attitude or preferences in the area of new technology in clinical trial processes.

1.5 Aim and Methods

The aims of this research are to show that new technology systems developed during the course of the project based on the new paradigm will:

1. Fulfil the three aims stated initially for the implementation of new technology.
2. Be preferred, by the users, over paper based collection systems.
3. Demonstrate the 'proof of concept' of systems in the new paradigm.

In order to do this the current technologies are evaluated and measured to produce a baseline performance figure. Several prototype new technology based systems are then developed based on ethnographical user centred design. These prototypes are tested in live clinical trials or other contextual settings. Performance is again measured and compared with the baseline figures from the current systems. In addition each user is asked to indicate their subjective preference for either the new technology or the current technology.

At this 'proof of concept' stage of development the aim is not to create finished systems that can be empirically compared with other systems, but only to show that the concept is valid and worth further investigation and development.

2. ANALYSIS OF PREVIOUS RESEARCH.

2.1 The Quality Assurance Process

The main problem with paper CRFs is the quality assurance process needed to identify and remove errors introduced at various stages of the data collection process. The Investigators introduce several kinds of error. The most frequent error calculated from categorisation of the number of DRFs sent is missing data. In studies on reasons for DRFs, Siegmann (1997) and Kampfner (1998) found that missing data alone accounts for between 40% and 50% of data requests. Other errors made by the Investigator include data written unclearly, data in a language other than English, values entered in the wrong place or simply an incorrect value. Fritz (1997) calculated the error rates for all types of error made by the Investigators through different times in a trial. At the beginning of the trial he registered up to 42/10,000 data points (dp) due to learning the CRF. During the main part of the trial there were between 10/10,000 dp and 24/10,000 dp with an average of 13.5/10,000 dp. Another study presented by Rudloff (1997) of two trials showed an error rate of 120 and 150/10,000 data points respectively. No reason for this high number is given.

On paper forms the Investigators sometimes write extra information on the form in areas not provided for a response. This may well be because the Sponsor has not asked questions that the Investigator thinks are particularly relevant. According to regulatory requirements in the FDA[1] Guidance for Industry: Computerized Systems Used in Clinical Trials (1997) all data entered onto a CRF must be entered into the database but there is often no field in the database for such extra information. If such extra entries are allowed in RDE systems then the use of electronic 'post-it' notes has been used to provide a solution to the entry of additional information. The data in both cases cannot be analysed because it is unstructured. Where extra information has not been allowed Hodges *et al.* (1996) found that extra information was reduced from > 50% to nil.

The main benefit of RDE in the area of quality assurance is the ability for the computer to check the data as it is entered. The person entering can be prompted for missing data and warned if a data item appears incorrect. Redfield (1996) found that all current RDE systems have in-built error checking. However, this has been implemented badly in many systems. 'Hard' error checks have been used, that is to say the person entering the data can not continue until the correct entry is made. Crayne (1996), Epstein (1996) and Lawton (1998) have found in practice that hard error checks reduce the usability of the system. Epstein (1996) also found that the use of too many 'soft' error checks such as warnings and information messages could become very annoying eventually reducing usability. PMT607 (1990) identifies this as being a typical failure of a technology focus where the full abilities of the technology have been applied without knowledge of HCI factors.

Studies investigating the reduction in errors as a result of using RDE in the trial have shown large reductions. Hodges *et al.* (1996) registered a reduction from 100% of patients with inconsistent recordings when paper was used to 0% when an electronic data capture system was used. In a study by Mirgoli (1996) there was a 100% match between the data captured in the system and the source data, this after a 100% source data audit. Callahan-Squire (1996) reports an 80% reduction in errors returned in the data. Daniels (1996) uses a figure of 85% reduction in data queries returned to the site in financial justification for RDE.

[1] American Food and Drug Administration (FDA)

For the RDE system to be optimally effective, all error checks need to be programmed into the eCRF before it is sent to Investigators. Hammarstrøm (1997) suggests that this is a process change that provides problems for the Clinical Data Managers. She says that this is not possible because many of the errors are not known before the first data has been received. In traditional trials the error checks can be programmed at any time after the CRF is created and preferably, but not necessarily, before the first forms are received.

2.2 Monitoring

Before the completed paper forms can be returned to the Sponsor, they must be checked for the common types of errors. A person called the Monitor does the first stage of error checking. The Monitor is usually either an employee of the Sponsor or is from a Contract Research Organisation (CRO) hired by the Sponsor. If 40%-50% of DRFs result from missing data as suggested earlier, it is clear that the monitoring of the forms at this stage is not very effective.

Another Monitor task is to carry out ‘source data verification’. This is the task of comparing what is on the CRF with any original medical notes and other data sources. This can only be done by the Monitor at the site and cannot be done by a computer. The Monitor is also the liaison between the Investigator and the Sponsor and a computer cannot effectively replace this human contact.

Callahan-Squire (1996) suggests that with the in-built error checking in RDE systems it should not be necessary for the Monitor to check the data before it is sent from the Investigator although this does sometimes still happen. Source data verification of the computer data against the original source data will still need to be done and can only be done at the trial site.

2.3 Return of the CRFs or Data

It is desirable to get the CRFs returned from the Investigator as soon as possible after the patient has finished as a subject in the trial. This is important for several reasons. The earlier forms are returned and entered, the earlier errors can be identified and notified back to the Investigator. If the errors are being caused because of a misunderstanding, errors on subsequent patients can be avoided. Fritz (1997) calculated that this kind of feedback training could reduced errors from a peak of 1.4 errors per page at the start of the trial to a low of 0.25 towards the end. If data is quickly and regularly returned to the Sponsor throughout the trial only a few forms and a few errors will be outstanding after the last patient has completed in the trial. The time taken to get the last forms in, entered into the database and the last errors corrected directly affects the duration of the trial. This is because the database cannot be locked and the report cannot be written until all errors are removed.

With electronic data capture systems, as with paper CRFs, it is useful to get the data back to the Sponsor as soon as possible to check for errors generated through misunderstanding, a type of error for which the computer cannot check. Without the need for monitoring, the data can be sent on a more regular basis, nightly for example. In a fully connected system, DRFs could be sent back to the Investigator electronically to be corrected next time data is entered.

To achieve such communication all electronic data capture systems are equipped with the possibility for electronic data transfer. Most of these solutions use modems to communicate. The

most commonly used solutions are for the trial site to directly dial a computer at the Sponsor and send the data or for the Sponsor to phone the trial site and collect the data. This requires that the trial site have a telephone line capable of carrying international data connections. Callahan-Squire (1996) found such reliable telephone lines are difficult to get installed and maintained in many hospitals in Europe due to hospital regulations and old telephone exchanges.

2.3.1 Use of the Internet

The Internet has been tested as a possible solution to overcome the problem of intra-country communication links. However, in the pharmaceutical domain it has a number of disadvantages that currently outweigh the advantages. Early investigations into the use of the technology in this domain e.g. Abdulezer (1996), Kubick (1996), McPherson and Drabik (1996), Vincenzi (1998) highlight several issues. These include the tracking of information, data storage and structure, limitations of web technology, regulatory issues, data privacy, Web performance, everybody doesn't have it yet and Java is still too slow. International guidelines for transmission of regulatory data over the internet contained in the document ICH M2 ESTRI recommendations (1997) demand: "Secure EDI using either SMTP or MIME, digital signatures for authentication, data integrity and non-repudiation, compliance with applicable laws, e.g. 40 bits encryption in the US., key management, EDI tracking, and trading partner profile/agreement facilities". There is only one application identified in the guideline that conforms to these standards.

2.4 Sponsor Based Data Entry

With the paper based system, the CRF once returned to the Sponsor has to be entered into a database. Errors can be introduced into the database during the data entry process especially if the data entry interface is poorly designed. These errors must be removed in addition to any introduced by the Investigator. The data is normally entered twice, by two different people, a process called double entry, and then the two entries are compared for errors. Gibson *et al.* (1994) question the efficiency of double entry.

Table 2.1, *Levels of data point importance used to justify single data entry*

Category	Definition of the error	Examples
Vital	A major error on a principal end point	Large discrepancy in the date of death. "no recurrence" instead of "definite recurrence"
Important	A minor error on a principal end point or a major error on any other endpoint	"none" instead of "severe" for quality-of-life questions. "none" instead of "slight" for radiation pneumonitis
Less important	A minor error on any non-principal endpoint or on any other variable	"0" instead of "1" for WHO performance status. "none" instead of "slight" for quality-of-life questions
Trivial	An error which has no impact on the analysis	"Professor" instead of "Dr" for the title of the clinician. Upper case rather than lower case.

In a study, they found that by dividing the data points into four categories of importance, see Table 2.1, and concentrating more effort on the top two, the cost outweighed the benefit. The reduction in errors in these categories was only 2.5 in 10,000 dp.

From internal surveys, questionnaires and reports covering use of the data entry system currently in use by Nycomed, the following problems are highlighted. Alignment between the CRF and the data entry screens is poor due to flexibility of the data entry screen interface. Because of the complexity and misalignment between the CRF and the data entry screens a detailed set of instructions is required, the Data Entry Instructions (DEI). These appear to be seldom read, quickly forgotten and often confused with other DEIs. This adds to the number of errors. In complex trials it can take up to four days to learn the complexities associated with the data entry. Codelists are used to enable consistent data entry. Items on the CRF are coded before entry and only the codes are entered not the verbatim texts. A codelist may contain several dozen items of which only a few may appear on any one CRF. The extra items allow items not on the CRF to be entered by mistake especially where several items are similar.

2.5 Investigator Based Data Entry

Russell (1998) and Lawton (1998) describe a common expectation placed on RDE systems: that, as with paper CRFs, the Investigators would enter data themselves. If the Investigators check the data themselves as it is entered there should be no need for double data entry. Two of the studies on reductions in error rates showed that it is possible to achieve 100% correct data using RDE. However, it is not always convenient for Investigators to enter data into the computer directly in real time where it may be with paper because the environment may not be suitable. Environments where direct entry may not be suitable include patient consultations where Crayne (1996) has identified that a computer can become a barrier between doctor and patient. Other examples include where great concentration is needed such as a detailed examination of a patient or whilst operating complex machinery. The Investigator also simply may not wish to enter the data directly as it is being collected. Investigators are chosen for their professional skills as doctors and not as computer operators. If a nurse or junior doctor is present, it may be possible for them to enter data instead of the Investigator.

If data is not entered directly by the Investigator the ability for the Investigator to correct errors as the data is entered has been removed and the ideal quality assurance process is not achieved.

If data is not entered in real time other forms of note taking are used and then the data must be entered later into the RDE system. In such instances, Spillar and Schoenfelder (1991) suggest using RDE screen printouts to collect the data. They call these ‘Pseudo CRFs’. However, this data entry then becomes more an administrative task and is often seen as a duplication of effort that Epstein (1996) suggests the Investigator may hand to a more junior doctor or other hospital staff. If this is done then it is no improvement on the paper based system and the data must still then be checked either by the Investigator or another form of verification must be used. The only ‘advantage’ is a shift of the burden from the Sponsor to the trial site.

Epstein (1996) and Russell (1998) have found that filling out an electronic CRF takes longer than filling out a paper CRF and this is a point that has not been lost on Investigators. If an eCRF takes only 3 minutes longer to fill out and the Investigator sees 20 patients in a day that is 1 hour of

extra work. If the Investigator is first doing data collection on pseudo CRFs and then entering it into the RDE system, this is even worse. For a busy Investigator, this is unacceptable.

2.6 Portability

Paper and pen is an inherently portable medium for collecting data, computers on the other hand are not so convenient. To achieve the ideal process of data being entered in real time the Investigator must be able to have the computer available at the appropriate times. For this to be possible palm-top computers with handwriting recognition for each Investigator have been tried. Papers by Frankish *et al.* (1995) and Mirgoli (1996) have shown that the users accepted this technology. Papers from Mackenzie *et al.* (1994) and Carroll (1996) show that it produces disappointing results because of high error rates and was not acceptable. Mirgoli also points out the high error rates. The picture portrayed in Table 1.1 (page 3) of practical application in the pharmaceutical industry suggests that for clinical trials the overwhelming majority, 90%, of those who have tried it have decided not to continue using it after testing.

2.7 Electronic Laboratory Data

An example of a system that fits into the new paradigm is the electronic transfer of laboratory test data described in Tucker (1996). Data is collected by the laboratories from testing equipment directly into a computer, reformatted into a standard format and transferred digitally to the Sponsor. The Sponsor will then load the data into its own clinical database using another conversion program. The standard data format was developed by the Association of Clinical Data Managers (ACDM) and is in use by many laboratories and pharmaceutical companies throughout Europe.

2.8 Doctors, CRFs and Computers

The Investigators themselves dislike paper CRFs which are described in Epstein (1996) as complex and disorganised, ambiguous, tedious and time consuming, redundant and a storage problem. He continues; they interfere with patient enrolment, lower data quality, increase audit costs, delay completion of the trial and therefore delay submission of the New Drug Application (NDA)[1].

Designing computer systems for use by doctors appears to present special problems. Lewis and Rieman (1993) found that doctors would invest very little time in becoming familiar with a new system. Coble *et al.* (1997) writes “Due to past (less than successful) experiences with introducing information systems for physicians.....[the software] must truly meet the needs of the physicians in a highly usable manner”. Wilson, C. (1997) mentions problems with consultant physicians. Problems involved political issues of superiority as well as the quality of consultant’s handwriting.

[1] A New Drug Application (NDA) is the American equivalent of the marketing application used in Europe.

Doctors, especially those used as Investigators, are usually highly paid and very busy. Any system implemented must either save them time or give them something in return. Systems developed so far for RDE appear to do neither of these.

3. METHODS OF EVALUATION

3.1 System Development Methods

The methods used for the development of the prototype systems are chosen to reflect the belief in the abilities of the user to contribute meaningfully to technological change. Drucker (1998) reminds us of the time when "The wisdom of the experts prevailed". He and others were surprised to find that workers were neither "Dumb oxen nor immature nor maladjusted" as Taylor and Mayo had maintained earlier. Development of IT systems has been and still is to a large extent dominated by this old attitude. The development methods used are selected to demonstrate to the users how they can be involved in the hope that the positive experience and outcome will change their perceptions not only of computer systems but also of systems developers.

3.1.1 User participation

Hyclack and Kolchin (1986) and T833 (1995) are examples of literature that suggests user participation in systems design will result in a higher chance of a successful implementation. There is also much written on *how* to involve the users, e.g. Shackel (1989), Preece *et al.* (1994), Chin *et al.* (1997), Wilson, S. *et al.* (1997) and Mumford (1997). Each author suggests a different role for the user, from Wilson, S. *et al.* (1997) where the user becoming a designer to, as Shackel (1989) suggests, the designer becoming a user. Where there are such differing views it is unlikely that one is better than another, all are valid in their appropriate contexts. A merging of the two roles by breaking down the artificial barriers and using the full skills of all the individuals involved will be used in this project.

Participatory Design (PD) as discussed in Chin *et al*. (1997), Blomberg and Henderson (1990), Clement and Van den Besselaar (1993), Carmel *et al.* (1993) and Greenbaum (1993) is a broad user participative methodology with no agreed definition. Blomberg and Henderson (1990) suggest there are three tenets that guide practitioners: the goal is to improve the quality of working life, the orientation is collaborative and the process is iterative.

Figure 3.1 shows the position of the user in this project. It is a Human-Centred model created to show the relationship between the user, the project, the business environment and methods of Human-Computer Interaction.

The model shows that the stimulus can come from outside in the business environment or inside from the users. The whole change process is cyclical because once a new system is introduced the user's reality has changed and the new reality causes new problems and therefore new stimuli. This constant change is why participative methods of development are necessary in order to develop system that meet the users changing needs.

PMT607 (1990) identifies the kind of output to be expected from 'soft' participative methods as more a decision on *what* to be designed rather than *how*. This suits the purpose of the project.

A high level of user participation is necessary because the systems to be developed will be implemented into live clinical trials and it is essential that the users are clear over the design and functionality and the possible effects.

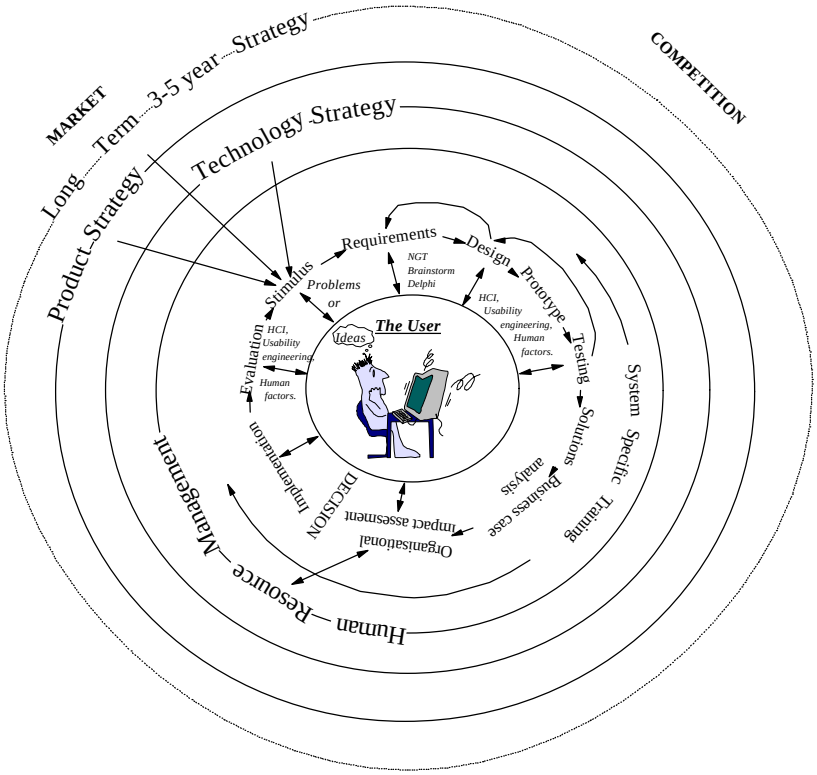

Figure 3.1, *The position of the user in Human-Computer Interaction*

3.1.2 Prototyping

Participative Design uses mock-ups and other paper based simulation rather than hands on prototyping. However, in T833 (1995) it says that users are “Happier adopting what they can actually see working – and when they can see for themselves exactly how it is an improvement on the existing setup”. Beeby *et al.* (1997) suggest that contextual prototyping provides one of the most obvious ways for the ‘client’ to be involved in the exploration of new concepts. The use of contextual prototyping allows the user to experience the potential new technology systems that may change their daily working life. They can then make judgements based on facts and not just guesses and opinions that may be based on previous bad experiences or the experiences of others. A method involving iterative prototyping is the User Software Engineering (USE) methodology of Wasserman and Shewmake (1985). Their goal is to involve the users *effectively* in the early stages of development. An excellent example of testing prototypes in context can be studied in Gould *et al.* (1987) where they used the approach to develop the Olympic Messaging System (OMS) for the 1984 Olympic Games. Many unexpected problems were experienced first hand and could be corrected and re-tested.

Prototyping is necessary in this project to measure system performance and user preference.

3.1.3 Ethnography

Ethnography is mentioned in Preece *et al.* (1994) as having a growing relevance in new technology implementations. There is a need for the developer to understand the users’ tasks and environment much better than is often the case. Mumford (1997) uses ethnographic data

collection techniques in the ETHICS (Effective Technical and Human Implementation of Computer Systems) approach to IT implementation and suggests it is a very valuable technique.

Ethnographic interaction with users allows data collection to be a near full time activity. The data collected is highly unstructured but extremely valuable. Problems which may not show up in a short period of evaluation can often be identified. Data collected can be either quantitative or qualitative.

This type of data collection for evaluation of computer systems is closely linked to the concerns for contextual evaluation versus laboratory based evaluation and the different ways to involve the user. The Ethnographic approach is closest to the developer becoming a user as suggested in Shackel (1989).

3.1.4 Contextual development

PMT607 (1990) suggests that recently the emphasis on laboratory testing has been the subject of much critical discussion. This and Preece (1993) both reference Whiteside *et al.* (1988). There it emphasises the need for contextual design, where the design and evaluation are moved out of the laboratory and into the users' environment. Landauer (1988) also strongly emphasises the need for cognitive psychology to be carried out in a contextual setting. It must never be forgotten that the 'H' in HCI is 'Human' and not a modelled approximation of one!

3.2 Data Collection Techniques

Data collection techniques are based on Table 3.1 (reproduced from Preece *et al.*, 1994, Table 29.1, p.611) and a discussion in M801 Study Guide (1996, p.44). In the early stages of system development it is important to get as full an understanding of the real world of the application domain as possible. The M801 Study Guide (1996) mentions questionnaires and interviews as being used in the 'softer' sciences such as ethnology and in projects for the introduction of new technologies. This project combines these two aspects. The primary methods will therefore include these and other survey methods the results of which will be qualitative as opposed to quantitative.

Table 3.1, *Relationship between kinds of evaluations and reasons for evaluation*

	Observing and monitoring	users' opinions	experiments and benchmarks	interpretative	predictive
Engineering towards a target	X	X			x
Understanding the real world	X	X		X	
Comparing designs	X	X	x		X
Standards conformance			X		

X = indicates a very likely choice. x = is less likely

The morphological analysis in Table 3.2 shows which data collection techniques are used in which evaluation.

Table 3.2, *Morphological analysis of evaluations, objectives and data collection techniques*

Technology	Objectives	Data collection techniques
Paper and Pen	Baseline performance - speed Baseline performance - error rates	DRF data logs Activity timing Activity simulation CRF archive examination
Terminal based application (Clintrial 3.3)	Baseline performance - error rates Baseline performance - speed	Heuristic analysis [1)] Historical Questionnaires and Surveys Error logs Data listings Controlled experiment Activity timing
GUI Interface (MS Access 2.0)	Usability for data entry in-house or remote Preference comparison - GUI interface vs. terminal interface Performance comparison - speed Performance comparison - error rates	Direct observation Think aloud Interview Data listings Controlled experiment Activity timing
Video review form (MS Access 2.0)	Usability for direct entry EDC Preference comparison - computer vs. paper and pen	Direct observation Questionnaire
Spreadsheet for highly repetitive data (MS Excel 5.0)	Usability for remote data collection Preference comparison - spreadsheet vs. paper and pen Preference comparison - data conversion vs. data entry Performance comparison - speed Performance comparison - error rates	Questionnaire Activity timing Data listings
Courier	Usability for transport of the CRFs Baseline performance - speed Baseline performance - reliability	Survey Contract delivery speed
Modem - modem	Reliability of modems for data transfer Performance comparison - modems vs. courier	Survey
ISDN	Reliability of ISDN for data transfer Reliability comparison - courier vs. ISDN Reliability comparison - modems vs. ISDN Performance - ISDN Performance comparison - courier vs. ISDN	Survey for internal report User requests to helpdesk
Investigator survey	Usability of computers for data capture Preference comparison - computers vs. pen and paper Extent of use of new technology	Questionnaire

1) Heuristic analysis, (Nielsen and Molich, 1990)

A variety of different data collection techniques are used. Activity timings, data logs and experimental techniques will gather quantitative data. Questionnaires, surveys and observation will collect qualitative data.

3.3 Evaluation Measurements

Nielsen and Levy (1994) describe usability in terms of two measurable usability parameter categories: subjective user preference and objective performance. Measurements will be made in both of these categories.

3.3.1 Preference measurement

Our preference towards one thing over another, be it a brand of dog food or the colour of a new car is highly subjective but preferring one over the other will probably not have long term major consequences. However, the choice of a computer system which the users perceive as less usable than another with similar performance can make a difference. Preece *et al.* (1994) believes that "…it is important to find out what they [the users] think about using the technology. However good users' performance scores are when using technology, if they do not actually like using it for some reason it will not be used". Nielsen and Levy (1994) show that there is a good chance of picking the better system based solely on users' opinions. Nielsen and Levy suggest that these opinions must be gathered through actual use of the systems and not just what they think they would like before testing them.

There is a difference between measuring the system and measuring the user perception of the system. This is described in Oppenheim (1992) as the measurement of things 'out there' or 'inside', referring to the measurement of the tangibility of the real world or the intangibility of the human mental processes. For the measurement of tangible things he suggests objective measures and for the intangible he suggests subjective measures. There is a movement towards the objective measurement of mental processes in the human sciences but Oppenheim (1992) believes there are losses in this approach and rejects it suggesting that the losses may outweigh the gains. The majority of literature suggests that in the Information Technology (IT) field subjective measures are used in the majority of evaluations, e.g. Kokol (1997), Trihajuwidjajani *et al.* (1997), Akomode (1997) and Bennetts and Wood-Harper (1997). Probert (1997), however, puts the case for more objectivism. Nielsen and Levy (1994) found only subjective measurement of user preferences and objective measurements of user performance in a metaanalysis of 405 system evaluations.

The SUMI (Software Usability Measurement Inventory) system described in Kirakowski and Corbett (1993) and Kirakowski *et al.* (1996) measures perceptions of usability at three different levels of detail. The highest level is a "Global usability reading" generated from individual responses to 50 questions. This generated overall score should match the results of a single question if it were asked of SUMI participants. Financial constraints excluded the opportunity to use the SUMI system, which is marketed as a commercial product.

User preference will be measured by a single simple variable. Each user in the evaluations of new technology systems is asked to indicate whether they perceive this new method to be 'better' or 'not better' than the same task with the current paper based systems. It is not intended to measure

the usability of the systems, the ‘out there’, but the preferences of the users, their ‘inside’. The measurement of preference is performed as much to show that the users perceive the new technology as an improvement as it is to encourage active and willing user involvement in the developments. This is a fundamental of the participative development methodology used in this project.

3.3.2 Performance measurement

Because most financial managers of large businesses would be unlikely to risk investment of potentially large sums of money on such ‘intangibles’ as feelings and perceptions it is also necessary to measure tangible items upon which financial savings can be calculated. It is therefore also necessary to measure performance.

Performance is measured for data entry or collection speed in data points per minute (dp/min) and an error rate in errors per 10,000 data points. These two metrics are suitable to measure the change in the quality assurance process and the resource use and to estimate trial duration reductions.

3.3.3 Additional information

In addition to the data collected for the performance measurements and the subjective preference measurement, other data was collected from questionnaires, surveys and observations. Because the aim is not to measure the usability of the systems or to measure the users attitude towards the systems this data is included as additional supportive information only. Such data gathered during evaluations of current systems will be used in the design of the new technology systems. Data then gathered during the evaluation of these will be used to confirm that the new designs have succeeded in overcoming the problems identified and will also be used in any subsequent developments leading from this research.

3.4 Evaluation Participant Selection

Selection of the participants for the evaluations was largely imposed as a result of the trial into which the new technology would be implemented. The Clinical Data Managers and the Investigators were selected as part of the clinical trial and not for their use of new technology. Where internal staff were used in the comparison of data entry interfaces, all staff available at the time were involved. The staff during the period changed and it was therefore not always possible to do a perfect paired comparison.

3.5 Rationale Behind the methods

After ten years of new technology experimentation in data collection, it is only in use in a minority of trials. This project has suggested a new paradigm and this new paradigm has to be tested. Systems developed from the new paradigm must show that they are an improvement over the ways in which the majority of trials operate. The performance measurements will make this possible.

At such an early stage in the development life cycle with prototype systems, encouraging the active participation of the users is deemed to be as important as the measurement of performance and detailed factors of usability. The simplicity of the preference measure serves this purpose.

The aim is to gain the trust and interest of the users at an early stage. For users to be committed to the change process associated with new technology implementation, T833 (1995) suggests that as well as seeing the system working, they must perceive it as an improvement over what they already have. Oppenheim (1992) suggests that behaviour is more often determined by subjective impressions than by objective facts. It is one thing for the system developer to have measured the users' attitude towards a system and then tell them how they scored. It is another thing entirely for the users themselves to have made up their own minds based on their own observations, experiences and feelings.

Detailed evaluation of design features and usability would be a part of any subsequent development based on the results from the prototypes.

4. EVALUATION DESIGNS

4.1 Completion of Paper CRFs

These evaluations will identify the cause of errors and measure error rates caused by the Investigators when completing paper CRFs.

4.1.1 Manual Completion of CRFs

Measurements for filling in this form with the test data were made whilst simulating the Investigator asking a patient questions and/or looking up data in a patient journal. Ten forms were completed by different people. Entry speed performance was measured by timing with a stopwatch.

As an indication of the number of errors made by Investigators filling in the CRFs a summary and categorisation of the number and reasons for DRFs in four trials was made. The trials were selected from all trials that were being conducted in the evaluation period and were the only four considered to be representative of the 'average' trial conducted in my employer's area of research[1]. The categories are chosen to identify errors that should have been identified in the monitoring and those that could not be avoided. In addition to these four trials, information was collected from other trials and sources with known numbers of DRFs.

Another 'error' that Investigators make is to provide information not requested that they feel is possibly relevant or important by writing this in the margins and other areas on the form. As a measure of this a random sample of CRFs from the archive was examined. A total of 100 CRFs were examined that had been filled in by 20 different Investigators chosen at random from 6 random trials. Randomisation was performed by selecting from different sections of the archive room. The result is presented as a percentage figure of the number of Investigators who made extra comments on the forms.

4.2 Data Entry System Problems

The evaluations of data entry systems will measure error rates and entry speeds for data entry of paper CRFs through a terminal based data entry system, these being the current 'technology'. A new system for data entry will be created which can be used for in-house data entry or on-site data entry for remote data capture.

The evaluations of data entry technologies involved creating a standard CRF and a set of test data. The CRF used is a CRF called the Master CRF. This is a CRF containing standard pages used unchanged in the majority of trials. The Master CRF and Master data entry screens are part of the central library of company standards. The test data set (Appendix 6) was created specifically for the evaluations and is representative of the type and quantity of data captured during the types of research carried out by Nycomed.

[1] The 'Average' trial is based on calculations of average patient numbers, numbers of centres and number of CRF pages in trials conducted over the last four years.

A page section from the Master CRF in the CRF design application can be seen in Figure 4.1.

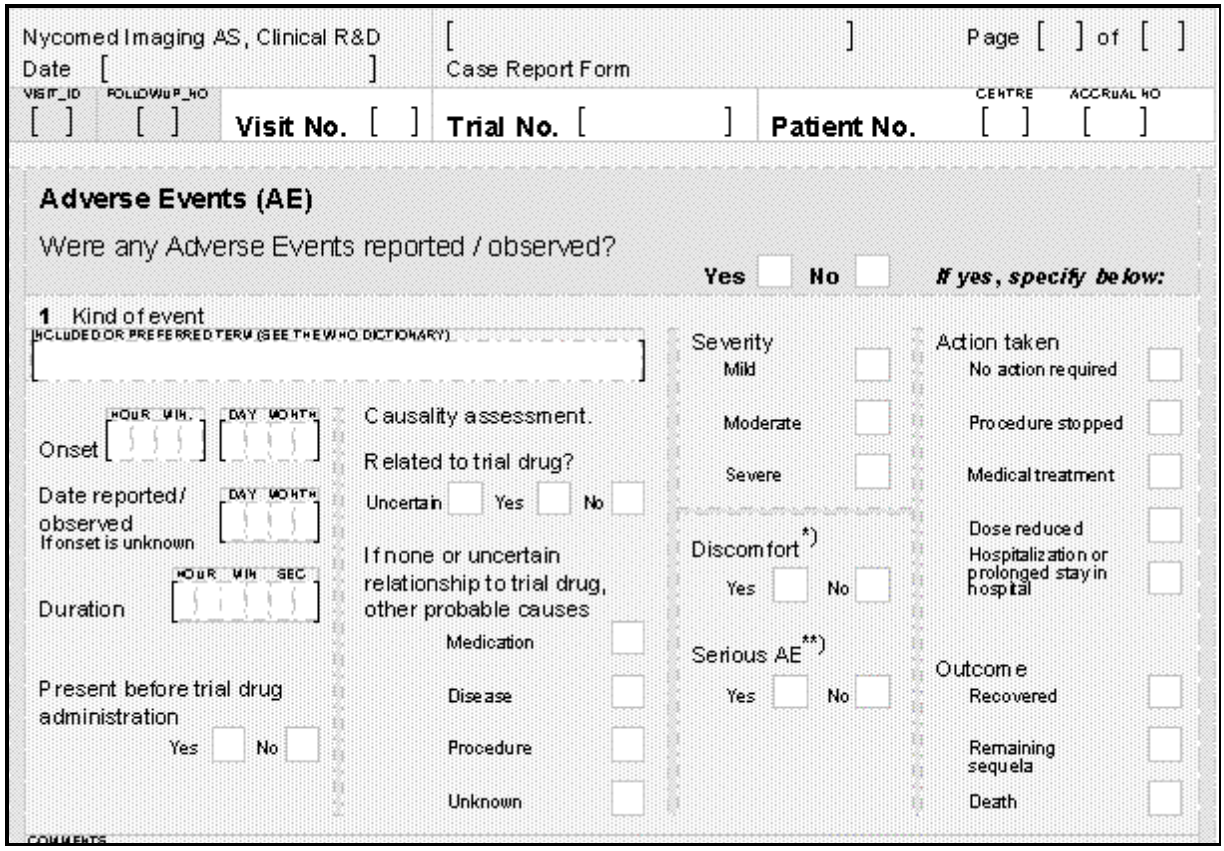

Figure 4.1, *Example Master CRF page - Adverse Event*

4.2.1 Terminal based data entry

The current technology for data entry is a terminal based application called Clintrial, version 3.3. The application is running on an AlphaVAX platform and is accessed through a PC terminal emulator program, Reflection4. The Clintrial application, its use and usability has been the subject of several internal surveys and questionnaires recently due to a growing awareness of its limitations compared to more modern systems. The reports resulting from these were studied in order to provide background information on the problems to be expected. Repeating the surveys would have been unpopular and unnecessary. A summary of the main problem areas is provided in Appendix 1.

Usability of the data entry system's user interface was evaluated by a heuristic analysis with heuristics based on those defined by Nielsen and Molich (1990). The heuristic analyses evaluated the interface in the following categories.

1. Simple and Natural Dialogue
2. Speak The Users Language
3. Be Consistent
4. Provide Feedback
5. Provide Clearly Marked Exits
6. Provide Shortcuts

7. Good Error Messages
8. Provide clear on-screen-help or visible access to on-line-help
9. Each action should function as expected by the user i.e. be intuitive

The first seven of the categories are from Nielsen and Molich (1990). The final two are added for the project in order to cover more modern features of computer interfaces. Direct observation of users during data entry was performed to confirm the findings from the heuristic analysis.

Data entry performance and usability were measured with the Master CRF and the test data set.

The participant sample for this evaluation was taken as all the available Clinical Data Managers and data entry staff employed at the time.

Each participant was given a copy of the Master CRF filled out with the test data and asked to enter this into the database using the associated standard Master CRF entry screens. The form used for entering the data from the Master CRF page (Figure 4.1) is shown in Figure 4.2.

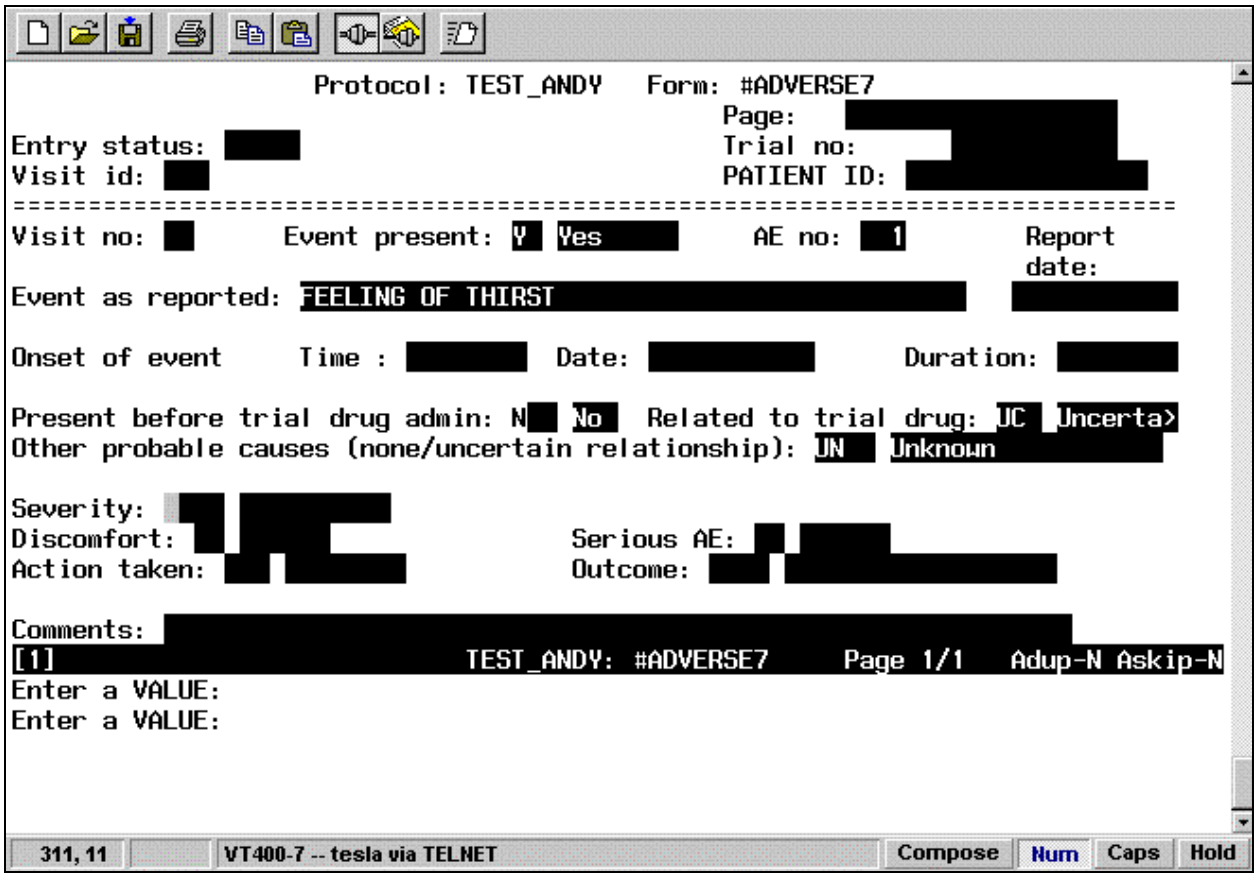

Figure 4.2, *Example data entry screen from Clintrial Master CRF form - Adverse Event*

Each participant was asked to record the time taken to do this. The data entry was done by each participant in his or her own office on their own computer.

The resulting database was listed out on paper to count the number of errors.

In addition to measuring the error rate for the Master CRF data entry, error logs were collected from data entry performed for real trial data and analysed these to get an error rate measured in numbers of records containing errors. Clintrial only reports the number of records containing errors and not the data point error rate. This result was converted to an estimated number of errors per 10,000 data points using average figures for the number of data points per record in the test data set.

4.2.2 GUI based data entry

The main design consideration for comparison with current technologies is the alignment between the CRF and the GUI designed eCRF. An improvement in speed and a reduction in errors should result by aligning the CRF and the data entry screens. This alignment should also result in the GUI system being evaluated as better than Clintrial 3.3. In addition trial specific code lists have been implemented by filtering the master codelists to include only items contained on the CRF.

To test data entry into a GUI based data entry system a set of data entry forms for the Master CRF was created in Microsoft Access 2.0. The corresponding screen to the Clintrial screen (Figure 4.2) is shown in Figure 4.3.

The evaluation participants were again all the available Clinical Data Managers and data entry staff. These were not necessarily the same as for the Clintrial 3.3 evaluation.

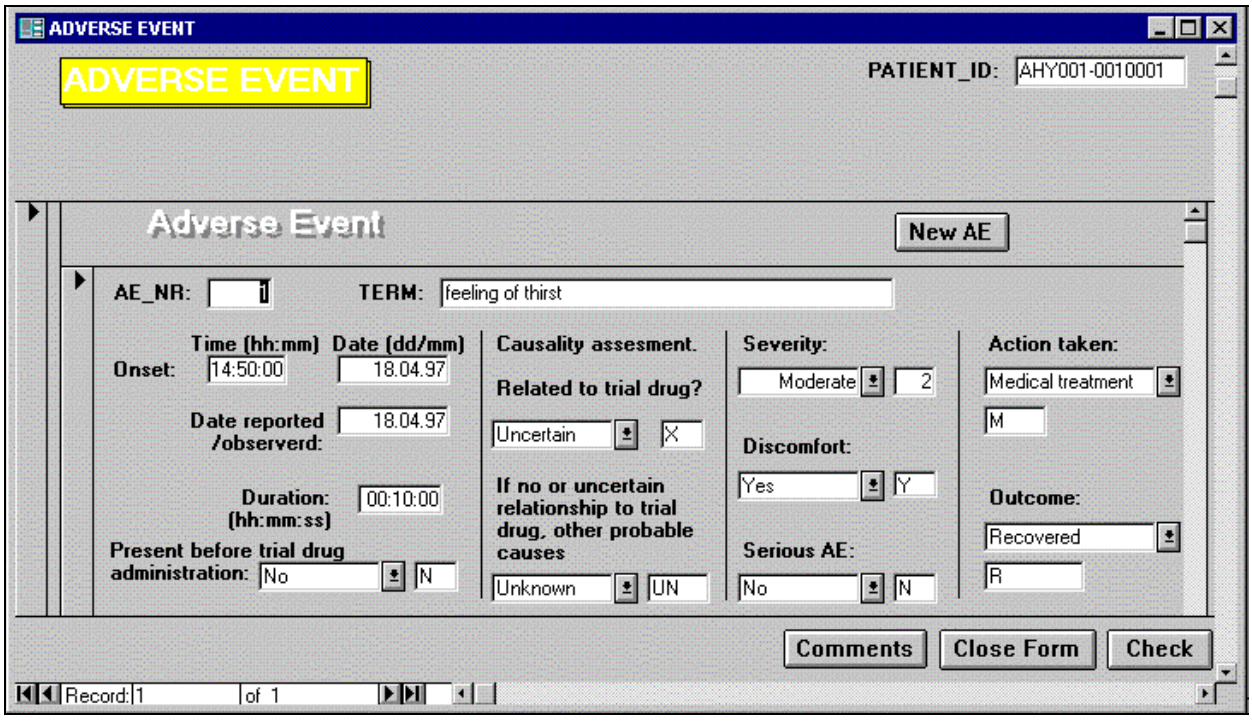

Figure 4.3, *Example data entry screen from GUI Master CRF form - Adverse Event*

The evaluators can be grouped as Clintrial data entry users and non-Clintrial data entry users. These groupings will be used to analyse the intuitiveness of the new interface based on the differences between the two groups. If knowledge of the data entry process is the primary factor then the difference between the two groups will be significant in both Clintrial and GUI. If

however the learnability or intuitiveness of the system is the reason for differences then with the GUI system there should be no significant difference between the groups. It is expected that the GUI interface system be faster for both groups.

The evaluation of this technology was conducted in the same way as the evaluation of the terminal based interface. Each user was given a Master CRF completed with the same test data as before. They were asked to enter the data and record the time taken. The resulting database was listed out to count the number of data entry errors.

To evaluate the usability of the system a number of the evaluation participants were directly observed during data entry, whilst being observed they were asked to think aloud. The comments were recorded as a basis for further refinement of the interface. Immediately after completion all users were asked in a simple interview to evaluate the new system as ‘better’ or ‘not better’ than the Clintrial system for data entry. Where there were specific problems the user was asked to describe the problems in more detail so that their comments could be compared with the direct observations.

A Student T-test was performed on the results of the data entry speed and data entry error rates to see if these metrics for the new technology were significantly different from the current technology. A non paired Student T-test was also performed on the data entry versus non-data entry user groups.

4.3 An Environment for Remote Data Entry

There are still environments where remote data entry is suitable. One such environment is the capture of data from the image review procedure within clinical trials. In order for an Investigator to make a final diagnosis and evaluation of the new drug or product he or she will review the pictures taken by x-ray, MRI or other modality. These pictures are called images in clinical research. This is done in a known environment, an image review room, where having a computer available for data entry is not a problem. This system therefore fits the new paradigm. The evaluation aims to show that a simple form for use in this setting will allow data to be captured and will be considered by the Investigators as better than paper.

4.3.1 Electronic CRF for image evaluation data collection

The technology evaluated for direct entry by Investigators was an electronic CRF (eCRF) . The evaluation was conducted as part of an Investigator’s meeting for the trial in which Imagine had been used (c.f. section 4.5.3). The Investigators were reviewing video footage of an Ultrasound examination. All Investigators present took part in the evaluation. They had to view the video footage and complete the eCRF, a page of which is reproduced in Figure 4.4.

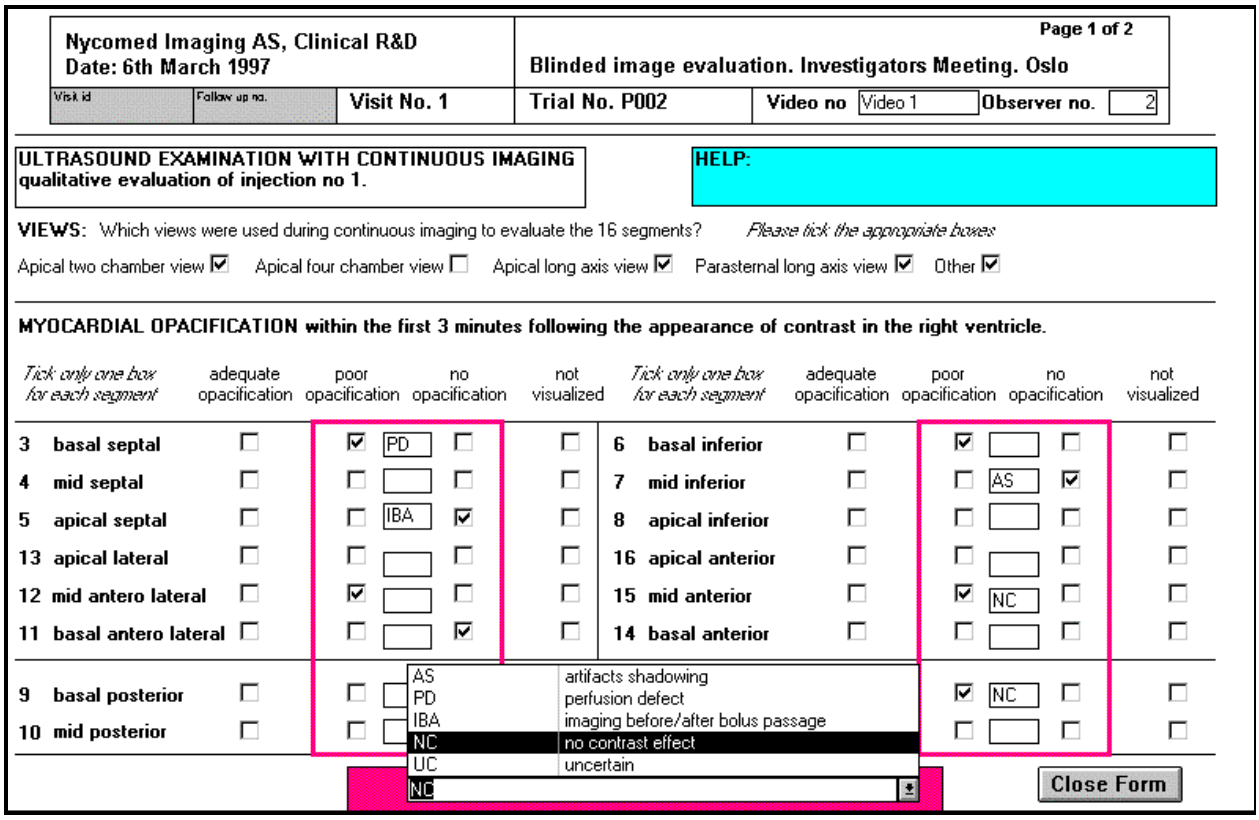

Figure 4.4, *Data entry screen in Microsoft Access for independent video review.*

A measurement of data entry speed was not relevant in this situation as the speed was determined not by their typing speed but how quickly they could evaluate the video footage. It was important that they could complete the forms in the time they were given to view the video. It was not possible to estimate an error rate due to time limitations at the meeting.

Usability of the system was evaluated by direct observation and the Investigators were asked to complete a questionnaire after the evaluation. In this questionnaire was the question asking if they considered this method better than paper or not. The questionnaire used is included as Appendix 11.

4.4 Escaping the Paper Paradigm

The creation of a system for the collection of technical and review data from a Magnetic Resonance Imaging (MRI) trial tested a system for escaping the paper form paradigm. This kind of data is highly repetitive and known to be a source of a high number of data entry errors. The system used simple spreadsheet technology, Microsoft Excel 5.0, to capture the data.

The aim of the evaluation is to investigate the usability of using spreadsheets for direct collection of repetitive data and compare the error rate and process speed with paper methods. The measure of preference will also be collected.

4.4.1 Spreadsheet for MRI data collection

Selection of the trial was made by request to the Clinical Research Co-ordinators for a trial which they deemed suitable based on a description of the proposed method of data collection. A single centre MRI trial with six patients was presented for the evaluation. In the trial 14 data items are constant for each MRI picture taken and then two measurements for each data record are the final results. The spreadsheet was constructed to match the database structure and formats into which it would be transferred to make this process as error free and efficient as possible. Figure 4.5 shows a section of the spreadsheet.

Study id.	Patient id.	Visit number	Exam no.	Picture series number	Sequence type	Region of interest	Scan Weighting	TR	TE
(Mxxx)	*(Mxxx-yyy)*	*(1,2...10)*	*(Pre or Post)*	*(1,2,3,...)*	*(SE, GRE TFE...)*	*(Liver 1, marker 1...)*	*(Text)*	*(Number) (ms)*	*(Number) (ms)*
M022	M022-001	1	Pre	1	FFE	Liver	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Pancreas	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Marker 1	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Marker 2	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Marker 3	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Marker 4	T1	100	4,6
M022	M022-001	1	Pre	1	FFE	Background	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Liver	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Pancreas	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Marker 1	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Marker 2	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Marker 3	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Marker 4	T1	100	4,6
M022	M022-001	1	Pre	2	FFE	Background	T1	100	4,6
M022	M022-001	1	Pre	3	FFE	Liver	T1	100	4,6
M022	M022-001	1	Pre	3	FFE	Pancreas	T1	100	4,6
M022	M022-001	1	Pre	3	FFE	Marker 1	T1	100	4,6
M022	M022-001	1	Pre	3	FFE	Marker 2	T1	100	4,6

Figure 4.5, *Section of the Microsoft Excel spreadsheet for Signal Intensity measurement*

Because this was a single centre trial there was only one Investigator and one Clinical Data Manager. These two were the system evaluators.

The Investigator was given a portable computer with the spreadsheet pre-installed and instructed on how to complete it.

The Investigator returned the data by diskette regularly so that it could be manually checked to ensure that he was completing the spreadsheet as expected. The final data was converted from its entered format into an ASCII file and transferred into the Clintrial database.

No automatic error checking was done by the spreadsheet but a manual check was made and a batch error check executed after data was transferred to the database. The performance of the manual check of the data, conversion into ASCII files and transfer was measured by timing each stage. Error rate and data transfer speed were compared with calculated manual entry of the same data.

The usability was measured by an e-mail questionnaire to the Investigator including a question to ascertain his subjective comparison between the new technology and paper CRFs for the same data collection as either better or not better. The questionnaire is contained in Appendix 10. The Clinical Data Manager on the trial responsible for the data conversion, transfer and error checking

was asked for his subjective comparison after the trial was complete as to whether this was either better or not better than manual double entry and correction of the resulting errors.

4.4.2 Advanced MRI spreadsheets

Another member of the systems development staff implemented this method of data collection in further trials, with modifications to the idea. The spreadsheets were 'enhanced' with some of Excel's more advanced features such as action buttons and drop down list box selections. Responses for subjective comparison were collected by a single question asked at the end of the trial by the system developer, 'better' or 'not better' than using paper for the same type of data collection.

4.5 New Technology for Electronic Data Transfer (EDT)

In order for electronic data capture systems to function ideally, full two way communication between the EDC system and the Sponsor is required. With most RDE systems modem to modem communication is built in. Integrated Services Digital Network (ISDN) will also be tested.

The aim of these evaluations is to compare the reliability, ease of use and speed of data transfer with the same metrics for the transport of paper CRFs by courier.

4.5.1 Courier CRF transport

The evaluation of the transport of the CRF by courier was done by a verbal survey of those involved in sending and receiving the CRFs. The result of reliability is presented as the majority opinion of reliable or not. The results of ease of use are summarised into a general opinion. The information on speed of delivery is taken from the contract with the courier and a measure of how well these time lines are kept is reflected in the measure of reliability.

4.5.2 Modem for data transfer

Once data is collected into a computer it can be transmitted from the remote computer to the Sponsor by modem over a normal telephone line. As a measurement of this technology's reliability a brief survey was conducted of Clinical Research Co-ordinators' success in connecting to our remote e-mail system from different locations around Europe and North America. The survey took the form of an informal set of questions of how many times they had tried and from where and how many times had been successful. There was no attempt to discover what they had done if the attempt failed.

4.5.3 Computer scanned CRF images with ISDN CRF transport

In order to evaluate Integrated Services Digital Network (ISDN) data communication this technology was chosen for a project involving the scanning of CRFs at the trial site. ISDN was required due to the large volume of traffic. Each scanned CRF was up to 4Mb.

The trial was an 11 centre multi-European country trial. Each centre was provided with a desktop flat bed scanner with automatic document feeder and each Monitor was equipped with a portable computer. The scanner was connected to a docking station in the trial centre where the computer was connected when the Monitor arrived. Also connected to the docking station was an ISDN data line. A deliberately rough diagram of the system used in presentations of the concept to users is shown in Figure 4.6. The users of the system and therefore the evaluation participants were the Monitors of the 11 centres. There were five Monitors in total, one each from Belgium, Norway, England, Germany and Austria.

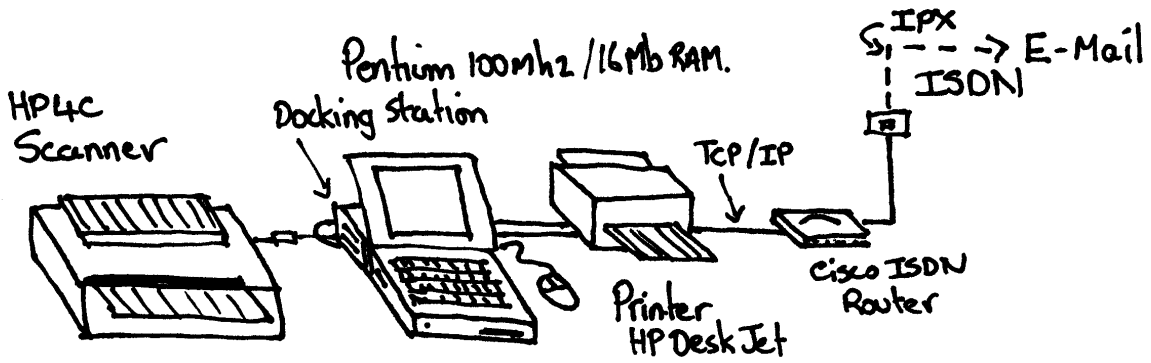

Figure 4.6, *The Imagine system as demonstrated to the users.*

CRFs were scanned by the monitors after having been checked and then attached to an e-mail and sent to the entry centre over the ISDN. The e-mail was sent using our company standard e-mail package, GroupWise.

Reliability of the ISDN link and ease of use of the scanning and e-mail system were the main metrics for this evaluation. The users were asked to summarise their experiences of using the system at the end of the trial for an internal report, these comments are used as the basis for evaluation of the reliability and ease of use. Transfer speed was measured during testing of the system.

4.6 Investigator Survey

To discover how many Investigators have used new technology in the collection of data in clinical trials and what they thought of it in terms of usability a questionnaire containing eight questions was created and sent to 147 of the Investigators used by Nycomed. A copy of the questionnaire is contained in Appendix 12. It contains six questions with yes/no responses, one required a year response and one was an open-ended question.

These Investigators do not only conduct trials for one company but may be conducting two or three trials on different products for different manufacturers simultaneously.

The results are presented in terms of the percentage responses to each question and the open question was categorised and presented as a frequency plot of the categories. The categories were selected as a result of the answers provided by the respondents.

5. RESULTS

5.1 Completion of Paper CRFs

5.1.1 Manual completion of CRFs

The simulated filling in of the CRF took an average time of 6m 50s (Individual timings are included in Appendix 4). There were a total of 108 data points written on each CRF and this equates to 15.8 dp/min.

Table 5.1 shows the number of DRFs sent for four trials. The reasons for the DRFs were categorised and it was concluded that a large number of the DRFs were avoidable. Avoidable is defined in these terms as missing information, wrong or illogical information and illegible entries. The overall average of avoidable errors is 85.5%. The two worst categories are missing data which accounts for 38% of the DRFs and wrong or illogical which accounts for a further 40%.

Table 5.1, *Summary of reasons for DRFs*

	Trial A		Trial B		Trial C		Trial D	
Number of DRFs *	42		45		38		40	
Missing info. *	13	31%	22	49%	8	21%	20	50%
Wrong or Illogical *	17	40%	16	36%	15	39%	18	45%
Illegible	4	10%	1	2%	6	16%	1	2,5%
Other causes	8	19%	6	13%	9	24%	1	2,5%
* Total defined as avoidable.	34	81%	39	87%	29	76%	39	98%

The number of data points in these four trials can be estimated from standard figures for the number of data points per page and per trial, the number of CRF pages per trial and the number of patients per trial. The four trials above had an average of 120 patients with a 20 page CRF. A CRF has on average 15 data points per page. Taking these figures this produces an average of 36,000 data points in each of the above trials. All four trials were of a similar design and size. With an average 41.25 DRFs sent this equates to an error rate of 11.5 errors / 10,000 data points.

Doing these calculations for other trials with known numbers of DRFs shows a figure from 10 to 18 errors per 10,000 is a reasonable estimate.

From the random sample of Investigators, 4 out of 20 had made extra responses outside those required. It appears that this phenomenon is Investigator specific. Those that do this appear to do it on many and sometimes the majority of their forms and in all trials where they are involved. Detailed results are shown in Appendix 3.

5.2 Data Entry System Problems

5.2.1 Terminal based data entry

The interface failed in 7 out of the 9 categories in the heuristic analysis. User language and consistency were the only two categories where it passed although “Consistently bad” was also a

comment. There is little help or feedback, meaningless error messages, no shortcuts and it is not at all intuitive for new or inexperienced users. Detailed results can be seen in Appendix 2.

One of the most common complaints of the data entry interface is its inflexibility. This causes problems of alignment between the CRF pictured in Figure 4.1 (page 20) and the data entry screen for that section of the CRF shown in Figure 4.2 (page 21).

Appendix 1 contains a summary of some of the main points raised in previous surveys of data management processes and the direct observations of the data management staff conducted to confirm these findings. The main problems are with the flexibility of the interface, especially navigation and the use of code lists. The navigation problem causes records to be missed or entered into the wrong place where screens are repeated. The code list problem causes data to be entered incorrectly. These observations confirm the findings of the heuristic analysis.

The evaluation of entry speed into Clintrial 3.3 with the Master CRF shows a large variation. The average was 17 minutes (95% CI. 15.4 - 18.6) with a range from 13 to 24 and one user who failed to complete the evaluation.

There were a total of 1940 data points on the 18 identical CRFs entered equating to 108 per CRF or per enterer. The average time taken was 17 minutes therefore the average entry rate was 6.3 data points per minute (Range, 4.5 - 8.2 dp/min).

Data is entered for different data types. Each data type has different characteristics. Some are simple cross boxes, some numbers and some long text items. This shows up in Table 5.2 in the different number and types of errors recorded. The comments data type is pure text and has the highest error rate. Indication is only cross boxes and returned no errors. The adverse event data is highly coded to ensure consistency across events and products and this has produced a large number of coding errors.

Table 5.2, *Data entry error rates (data point errors) - Clintrial Master CRF data entry*

Panel	Data points	Total Errors		Coding errors		Text field errors		Other errors*	
Adverse	578	26	4.5%	15		5		6	
Comments	54	12	22.2%	6		5		1	
Demographic	90	1	1.1%	-		-		1	
Indication	66	0	-	-		-		-	
Medical History	180	1	0.6%	-		1		-	
Medication	864	22	2.5%	-		18		4	
Visit	108	3	2.7%	-		-		3	
Total	1940	65	3.4%	21	1.1%	29	1.5%	15	0.8%

- Indicates no errors

* ‘Other errors’ include data not entered or data entered where it should not have been

The total error rate for all entered data was 340 errors per 10,000 data points.

In real trials, with the current system outputs, it is only possible to measure the error rate per record. Data is entered in batches with several batches for each trial. The average for all CRFs in

a trial and the minimum and maximum values for the averages of each batch are shown in Table 5.3.

Table 5.3, *Data entry error rates (record errors) - real trials*

Trial id	Patients	Records	Mismatches	Percent	Min%	Max%
V055	123	6366	550	8.6%	2%	18%
V056	137	9429	748	7.9%	2%	41%
V050	308	14079	964	6.9%	3%	15%
V051	319	15984	1335	8.4%	7%	11%
T006	2	485	60	12.4%	12%	
T017	16	3521	346	9.3%	1.5%	40%
T018	14	1049	36	3.4%	2%	14%
Total	919	50913	4039	7.9%		

The percent score is the average error rate for all patients. Min% is the minimum batch error rate and Max% is the maximum batch error rate.

Details of individual batches are contained in Appendix 5. The table shows that the minimum error rate is quite stable but the maximum error rate varies greatly. The process is not in statistical control according to the statistical theories of W. Edwards Deming in Walton (1986) because there is one result in trial V056 of 41% outside the upper control limit. In addition the process shows wild swings within the upper and lower control limits.

From the number of data points per record on the Master CRF it is possible to estimate the data point error rate. The average record error rate in real trials is 7.9%. At 5.7 data points per record, calculated from the test data set, this is equivalent to 1.4% of data points or 140 per 10,000. This is a minimum figure assuming only one error per record. If there is more than one, the figure will be somewhat higher. This figure does not include long text fields, i.e. comments, because these entries are not checked by the computer, instead they are manually proof read. Excluding text fields from the Master CRF evaluation results in a figure of 190 errors per 10,000 data points.

5.2.2 GUI based data entry

The application was designed paying special attention to main usability problems identified from analysis of Clintrial 3.3; CRF and screen alignment, restrictions to codelists and flexibility of movement within records and between forms. By paying special attention to these points there was an increase in performance as expected.

The evaluation of entry speed into the GUI system with the Master CRF shows variation from 8 to 17 minutes to enter the forms. The average is 13 minutes (95% CI. 11.7 - 14.3). With 1509 data points entered by 13 different evaluation participants this calculates to an average data entry point rate of 8.9 dp/min (range 6.4 - 14.5). This average data entry rate is 41% faster than the corresponding rate in Clintrial 3.3.

The differences between Clintrial data entry rates and the GUI system data entry rates calculated by a Student T-test are significant ($p<0.001$). The GUI system enabled faster data entry than Clintrial 3.3.

Table 5.4, *Comparison between data entry users and non data entry users*

	Clintrial 3.3	GUI system
Non-data entry users	21.8	14.6
Data entry users	14.4	12.3

The comparison between experienced data entry users using Clintrial and non data entry users using Clintrial and the GUI system is shown in Table 5.4. The non data entry users were on average 51% slower than the data entry users with Clintrial and the differences were significant ($p < 0,001$) but only 19% slower with the GUI system and still just significant ($p < 0,05$). Although the difference between non-data entry users and data entry users using the GUI system is still significant it is far less significant that with the Clintrial system. This result confirms that the GUI system is more intuitive than Clintrial 3.3 and will correspondingly reduce the learning curve for new staff. None of the users required more than 10 minutes to learn the application before starting to enter data. None of the users had major problems entering data that caused them to require assistance to continue.

Table 5.5 shows the error rates for the different data types with the new GUI data entry system. The error rate for the comments data type is still high and is not much reduced from that of Clintrial. Error rates in other data types are more than halved. The overall reduction is 53% and the non text field errors are reduced by 74%. Comparison with Clintrial 3.3 based on a Student T-test shows the difference in error rates to be significant ($p<0.01$).

Table 5.5, *Data entry error rates (data point errors) - GUI Master CRF data entry*

Panel	Data points	Total Errors		Coding errors		Text field errors		Other errors*	
Adverse	435	7	1.6%	1		4		2	
Comments	39	7	17.9%	2		3		2	
Demographic	60	0	-	-		-		-	
Indication	30	0	-	-		-		-	
Medical History	135	2	1.5%	-		2		-	
Medication	720	8	1.1%	-		7		1	
Visit	90	0	-	-		-		-	
Total	1509	24	1.6%	3	0.2%	16	1.1%	5	0.3%
Clintrial totals	1940	65	3.4%	21	1.1%	29	1.5%	15	0.8%

- Indicates no errors

* ‘Other errors’ include data not entered or data entered where it should not have been

The alignment between the CRF page for Adverse Event, Figure 4.1 (page 20), and the corresponding entry screen in the Microsoft Access 2.0 GUI application, Figure 4.3 (page 22) is much closer than was possible with Clintrial 3.3, although still not perfect. JetForm 4.1, the application that creates the CRFs and Microsoft Access 2.0 have a majority of the same controls making this possible.

All the users except one said that they preferred the new system over Clintrial 3.3. It had been intuitive and responsive. Because the screen layout and CRF were nearly identical it had been

easier to enter the data. The use of drop down lists for codelists, which include only items that are on the CRF, was an improvement over Clintrial.

The one person who thought that Clintrial was better thought that the GUI entry screens were too cluttered and complex and was never sure where the entry cursor was on the screen. Even so, the user produced one of the fastest times using the GUI system. Several users mentioned that finding the entry cursor had sometimes been a problem and that this caused frustration. Other than this there were no serious problems. Most of the observed problems and user comments from thinking aloud relate to differences between the layout and wording of the CRF and the entry screen. Out of 37 comments and observations 22 (60%) are categorised as alignment problems, 9 could have been solved with better on-screen help, 5 were due to inconsistency and one was categorised as illogical. Transcripts of the direct observations and the comments made by participants during the evaluation and the applied categories are listed in Appendix 7. These could be used to further improve the system.

All users when asked said that a system with this type of user interface would probably be suitable for real data entry.

Individual entry times and subjective comparison results are shown in Appendix 9.

5.3 An Environment for Remote Data Entry

5.3.1 Electronic CRF for image evaluation data collection

The important aspect of this system was that the Investigators performing the image evaluation could complete the review and capture the data in the time available unhindered by the data collection technology. Only 10 minutes were allowed for training immediately before the review commenced. Despite this short introduction all the Investigators managed to complete the video evaluation and complete the eCRF in the time they had available.

From observation during the evaluation none of the Investigators had difficulty in using the mouse and keyboard. The system could either be keyboard or mouse controlled or a combination of both, most chose to use a combination. Cross-boxes were selected with the mouse and reason codes were entered using the keyboard. None of the Investigators had to ask for help during the session to be able to continue.

Nine out of the ten groups of Investigators completed the questionnaire attached to the user instructions. Table 5.6 shows the results. In the usability questions (Q1-Q3) there are more positive than negative responses. Q4 is about expectations. The response shows that expectations are nearly equally divided. Q5 and Q6 seek to identify the Investigators' daily interaction with computers. All Investigators use computers every day and store their patient records on a computer, which is a very relevant point that will be discussed later. The final question, Q7, aims to add an outsider's view of the scanner system used by the monitors in the scanning with ISDN evaluation. The Investigators did not use the system directly.

Table 5.6, *Investigator survey at video review evaluation*

Question	Yes/ Agree	Not Sure	No/ Disagree
1) This method of capturing data is appropriate for blinded reads +	8	0	1
2) This method of collecting data can be used for any type of data	5	2	2
3) This method of collecting data is better than using paper	3	3	3
4) Computers will replace paper forms completely for clinical trials one day	5	1	3
5) I use a computer every day for my work	9	0	0
6) The place where I work stores patient or examination records on a computer	9	0	0
7) The data capture solution for the trial P002 was a good solution for the trial*	5	2	2

+ Blinded read is another term used for an image review. In a blinded read the reviewing doctor does not have any information about the patient and can therefore be unbiased in the review.
* The trial P002 used the Scanning and ISDN to capture CRF images and transport them.

In retrospect, question 3 is badly worded. The question as worded does not differentiate between the collection of data for video review from general collection by computer for all types of data. The result is not consistent with the result from question 1. The combination of these two questions suggests that the investigators preferred the new technology over paper although the comparative analysis will use the results as collected.

5.4 Escaping the Paper Paradigm

5.4.1 Spreadsheet for MRI data collection

The trial used for this evaluation was a single centre trial and therefore there was only one Investigator who used the system. The Investigator managed to complete the spreadsheets exactly as instructed. He chose to split the data up by creating and naming one file for each patient for each of two different patient groups. This he did on his own initiative and this made the information more manageable.

The manual quality control, coding and loading into Clintrial took two working days. This evaluation was a one off system but if it had been repeated the coding and loading routines would have been reusable resulting in approximately 2 hours required for manual quality control. Including these different operations the data entry rate equates to 35 dp/min. Actual time to load the data from ASCII transfer files into Clintrial took less than 1 minute, a speed of > 23,200 dp/min.

From earlier calculated entry speed and error rates it would have taken approximately 22 days at 5.5 hours per day to double enter and approximately 24 hours to correct the errors.

One cut and paste error was found repeated in all six of the patients' files. This was, however, on non-important administrative data. The total number of data points was 23,200 to the nearest 100. This equates to an error rate of 2.6 in 10,000.

The Investigator's responses to the short e-mail questionnaire were:

- Was the system easy to learn? Yes
- Was the system easy to use? Yes
- Was the system stable? Yes
- How was the performance? Slow
- Was it better than using paper? Yes

The Investigator made the additional comment that a system which connected directly to the MRI computer providing the data would be a very good idea. Appendix 10 contains the responses to the questionnaire sent to the Investigator.

The Clinical Data Manager responsible for the trial said that this method had been much better than data entry into Clintrial 3.3 with following manual data correction.

In addition, with paper forms almost 500 sheets of paper would have been required to collect the same information. This is an important consideration for the future.

5.4.2 Advanced MRI spreadsheets

The development of the spreadsheet data collection method was used in three further trials. Table 5.7 summarises the results of the subjective comparisons for these developments. In the first trial the spreadsheet contained list selection boxes and Visual Basic scripts. By adding the advanced features the ability to use cut and paste and repeat copies to create the repetitive entries was removed. This was the main design aim behind using spreadsheets. The Investigator evaluated the first spreadsheet as not better than using paper. Most of the automation was removed for the second trial and the Investigator evaluated it as better than paper. The third trial was a mixture of automation and manual copying of repetitive data and was evaluated as better than paper.

Table 5.7, *Advanced MRI spreadsheet preference comparison results*

Trial	Version of the system	Subjective comparison
Trial 1	Advanced functionality	Not better
Trial 2	Plain spreadsheet	Better
Trial 3	Combination	Better

5.5 New Technology for Electronic Data Transfer (EDT)

5.5.1 Courier CRF transport

Eight Clinical Research Technicians (CRTs) and Clinical Research Co-ordinators (CRCs) were asked to state whether the transport of CRFs by courier was reliable or not reliable. None of the people asked considered the courier used to be unreliable. The only comment as to the reliability of the whole process was that occasionally CRFs did not arrive when expected but this could often be tracked to the sending or the receiving post rooms and not the courier. The courier is considered easy to use. CRFs are packaged into batches and sent via the trial site post room.

CRFs from Europe are delivered with either next day or 48 hour service. CRFs from outside Europe are delivered with a 72 hour service.

5.5.2 Modem for data transfer

In the survey of Clinical Research Co-ordinators attempting to access the remote mail system whilst travelling, 44% of attempts failed. Table 5.8 shows where calls were attempted from. Even from our own offices in the USA it was still a problem to make a connection back to the e-mail server in Oslo.

Table 5.8, *Successes and failure of international modem communication*

Country	Location	Success	Failed	Total
USA	Nycomed offices	2	2	4
USA	Hospitals	1	2	3
France	Hotels	1	2	3
Germany	Hotels	2	1	3
United Kingdom	Hospitals	3	0	3
Total		9	7	16

There was no pattern to the countries where problems occurred although from the USA to Europe does appear to cause slightly more problems than within Europe. There was also no pattern to the types of locations, i.e. hospitals, hotels or our own offices in the USA.

The set-up of modems is complex. Knowledge of the ‘AT command set’ is required. The functions of the modem can be set to cope with different conditions but due to the complexities of national and internal exchange telephone systems this is usually beyond the average user.

5.5.3 Computer scanned CRF images with ISDN CRF transport

One centre refused the installation of an ISDN because they were engaged in a major upgrade of their internal communications systems to ISDN but not in time for the trial. One line was not installed before the trial started due to problems with the centre’s national telephone company but as it happened the particular centre did not include any patients before the line was installed.

All the ISDN lines functioned first time with the standard pre-installed set-up when the computer equipment was connected to the line.

A 24 hour help desk was available in case of technical difficulties with any part of the system.

No users called because of problems with the data communication. There was however one peak period overload on the ISDN lines at the end of the trial when there was a rush to return CRFs and DRFs where one user had to wait 30 minutes before gaining access.

The scanned CRFs which were up to 4Mb in size took 12 minutes to scan, 3 minutes to attach to the e-mail and 6 minutes to send. This is a total of 21 minutes per CRF. Each CRF was printed, taking 15 minutes, as soon as it was received at the Sponsor site and was therefore available to be entered in just over 30 minutes after being monitored at the site. This is considerably faster than by courier transport but also considerably more complex.

5.6 Investigator Survey

A total of 50 responses were received from the 147 questionnaires sent which is a response rate of 34%. One of the respondents had not satisfactorily completed the form. The results of the 49 properly completed forms are shown in Table 5.9. 53% of the Investigators asked had not used new technology but out of those 92% expect that new technology will be better than paper. Of the Investigators who have used new technology 87% think it is better. Only 5% therefore appear not to have their expectations fulfilled. Despite the high number that think it is better than paper a lower number, 74%, would use the same again. Of the 6 who would not use it again, 3 said it was not user friendly, 4 said it was not suitable and 3 said they did not like using it. Only one Investigator answered no to all the usability questions but he also said it was still better than paper! This possibly says more about the quality of the paper CRFs he is asked to complete than the technology he had used. 13 out of the 23 Investigators who had used new technology answered yes to every question.

Table 5.9, *Summary of Investigator questionnaire results*

Question	Yes		No	
Have you used new technology in data collection in clinical trials?	23		26	
	Yes	No	Yes	No
Did you consider it usable	19	4		
Did you consider it suitable	18	5		
Did you like using it	20	3		
Would you use it again	17	6		
Was it or do you think it would be better than paper	20	3	24	2

No meaningful results were obtained from the question regarding when the Investigators thought new technology would replace paper completely. The majority answer was year 2000. This is an unrealistic result and it is believed that the respondents have a mental picture of everything technological happening in the year 2000 without realising that it is only 18 months away.

Included on the questionnaire was an area for the Investigators to suggest what they think a system should provide to them such that it would benefit them. 27 of the 50 respondents provided a response to this question. The comments have been categorised to show their main concerns.

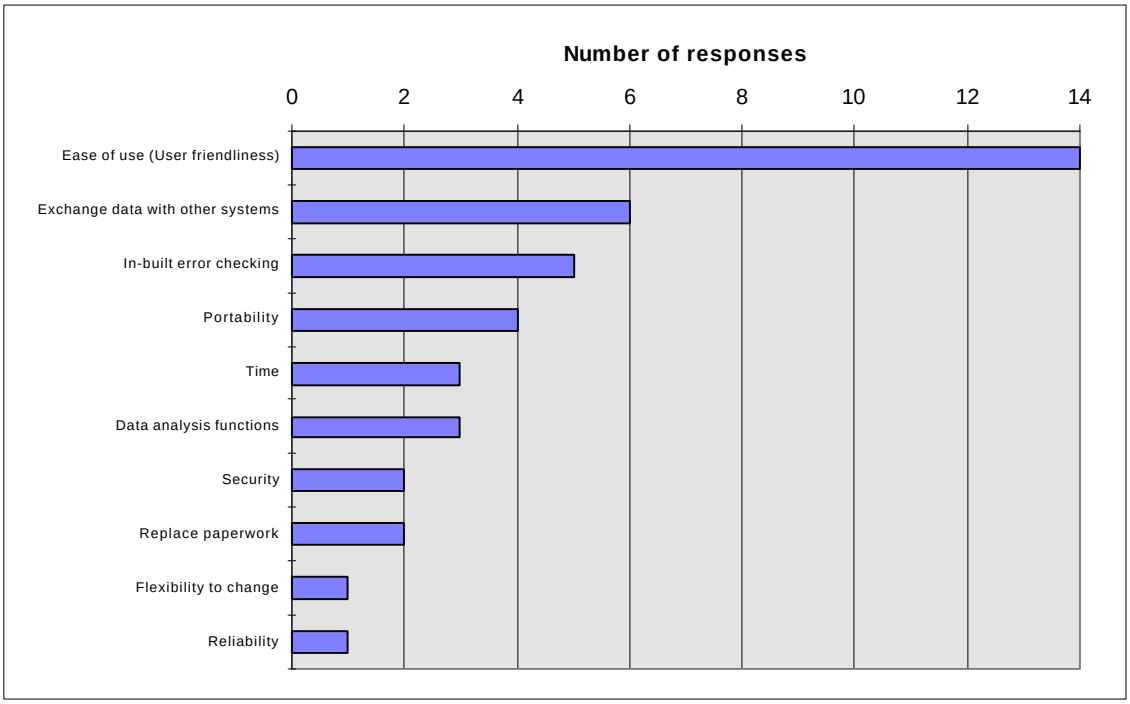

Figure 5.1, *Investigator survey - categories of concern*

Figure 5.1 shows the main concern to be usability, phrases such as “easy to use”, “the data entry form must be PERFECT!”, “user friendly” and “ease and quickness of entering data” describe this concern. Second to usability is the exchange of data with other systems, 6 out of the 27 responses contained comments in this category. This is a strong indication of the future as the Investigators see it. This view fits into the new paradigm suggested by this project. Appendix 12 contains transcript of all the comments received.

6. DISCUSSION

6.1 The Initial Problem

The problem in clinical research was to reduce the duration of clinical trials in order to get new products on the market faster and therefore remaining competitive whilst maintaining quality. This was to be achieved by an improvement in the data capture process in order to reduce data errors and therefore reduce resource use and trial duration. To do this new technology was applied to the data collection process, as this was a part of the process on the critical path identified as being suitable for computerisation. Several different technologies were tried to overcome problems in the paper based process from hand held computers to fax based OMR/OCR. After ten years however, only 5% of trials may be employing new technology. Nearly 90% of Investigators who have used the new technology in clinical trials say that it is better than using paper and that they would use it again. Pilot trials of the new technology have shown that implementation can reduce the duration of a trial by reducing the time from last patient completed to database locked on the trial's critical path. Each day's reduction in trial duration could mean an extra $1m opportunity cost. This figure should be a great enough incentive even to outweigh the cost of the equipment necessary to implement electronic data capture in all trials. (An overview of representative costs is given in Appendix 13). With all this in its favour, one would expect the pharmaceutical industry to be converting all its trials to the use of new technology but it isn't.

It is suggested that the problem lies in the way the old paper based process has been transferred into the new technology. By simply copying the paper case report form into an electronic case report form the benefits that computers and modern applications present have not been fully utilised.

Of the three main aims initially mentioned: to reduce trial duration, improve the quality assurance process and reduce resource use, it has been proved that there is an improvement in the quality assurance process and this results in a reduction in time to lock the database. There is no evidence to show that this reduction has led to a reduction in the duration of the trial or the resources used.

Ebsen (1998) suggests there is little evidence that electronic data capture saves the Sponsor money when looked at on a per-trial basis. The 'saving' comes later from getting the product to the market earlier generating revenue and hopefully profit. This is a systemic interaction that is only visible when a long term perspective is taken. If budgeting is done per trial, electronic data capture would never be chosen as a solution.

6.2 The Solutions

To show that new technology is an improvement over existing paper based systems and to prove the concept behind the new paradigm, prototypes were created for implementation in specific combinations of environment and data type. This is a fundamental of Human-Computer Interaction principles. The users were involved in all stages of development. This had to be done because the prototypes were being implemented into live clinical trials. The trial team leaders had to assure themselves that the system met the needs of their trial's data collection and met up to regulatory requirements.

The aim of all the solutions is to reduce the number of errors in the data returned from the Investigator. These errors should be trapped and removed during the monitoring stage but they are not. Results showed that missing data accounted for 38% of DRFs which agrees closely with the 40% to 50% suggested by Siegmann (1997) and Kampfner (1998). Wrong or illogical data caused another 40% of the DRFs and 15% of DRF were caused by illegible data. These together are the cause of 93% of the DRFs in the analysis.

In addition to the errors caused by the Investigator, errors are created in data entry. A new data entry system was created in a Windows GUI application in order to compare this with the terminal based application used for data entry from paper CRFs. This evaluation was made to show that data entry into a GUI application would indeed lower the error rate, allow data to be entered more quickly and be more intuitive. Results show that all three of the aims were met. In the new paradigm where different technologies are used for different needs, paper will probably still be used for some data types coming from some environments. It is therefore important to provide a data entry system that is designed for minimum error rates during entry whilst maintaining an acceptable entry speed.

The categorisation of user comments and direct observation showed there still to be a number of alignment problems. In any project to introduce a GUI based data entry system, more detailed usability testing to measure the interface and refine it would be necessary in order to reduce the error rate still further. The error rate of 160 per 10,000 dp is still high when compared with the figure of 100 per 10,000 dp of Siegmann (1997)and 25 per 10,000 dp of Gibson *et al.* (1994). It was decided to use the Master CRF unchanged for the evaluation and not all of the layout features mapped perfectly to the GUI application. If the system were to be developed further the Master CRF would also need to be redesigned to match the facilities of the new data entry system.

The GUI system proved to be more intuitive than Clintrial 3.3. This is important to reduce learning curve times for new and infrequent data entry staff. If the system were to be used as an eCRF for direct capture of data then a low learning time for the Investigator or other hospital staff is a critical design requirement.

The new technology application was clearly preferred over the current technology for data entry. Nielsen and Levy (1994) found that there was a correlation between preference and performance and also preference and error rates. Preferred systems show better performance and lower error rates and therefore visa versa better performance and fewer errors were attained with systems that were preferred.

The GUI application was tested as an in-house data entry system and therefore had active error checking turned off. Errors were logged to a log file that could be reviewed later. The error rate of 160 per 10,000 dp would have been considerably lower if error checking had been active and errors were corrected as data was entered. In built error checking can efficiently check for missing data, wrong or illogical data and illegible data. Therefore a maximum reduction of 93% in the number of DRFs could be expected from using the system for RDE where RDE is appropriate. The number of errors detected is only as good as the in built error checks and as Hammarstrøm (1997) pointed out it is not always possible to define all error checks before the data is received. Allowing for this, the figures of 80% in Callahan-Squire (1996) and 85% in Daniels (1996) for reductions in the number of DRFs would appear realistic.

There are environments and data types where electronic data capture can be used in the new paradigm. This was tested in the video footage evaluation. The data type for this type of evaluation consists mainly of yes/no questions and questions with pre-coded categorised answers. Creating an eCRF for this kind of data is simple. It is important that layout is clear and follows the expected task of the user. The system tested was used in a time limited situation and all Investigators captured data without problems. Normally an Investigator can use as much time as needed to evaluate images. eCRFs are appropriate only where completion of the CRF is not the time limiting factor. The results have shown that completing an electronic CRF is considerably slower than its paper equivalent.

A spreadsheet based system was used in order to test a system specifically designed in the new paradigm. Highly repetitive data was collected in a magnetic resonance imaging trial directly into the system. This was done with only 6 errors in 23,200 dp. This type of error could have been predicted because it was made as a result of copying blocks of data, which was the main design consideration. One respondent in the Investigator survey replied that he uses a spreadsheet on a Psion 3a palm-top PC to collect information for clinical trials. In order to be a future system error checking would need to be included. This with the advanced features of spreadsheets would be possible. The advanced spreadsheets showed that it was possible to add limited automation without penalising usability. The Investigator noted that it would have been nice to collect data directly from the MRI machine or review station. These technologies have proprietary data formats and collecting the data directly poses a number of problems. The future is in overcoming these problems and perhaps working towards a generic export format.

International data transfer has proved to be a problem in many studies. Cross border in Europe and from America to Europe. The small survey of clinical co-ordinators confirmed this. A new technology in communication is the digital telephone line or Integrated Services Digital Network (ISDN). This allows computers to communicate digitally through digital exchanges with high reliability. ISDN is an International Telecommunications Union (ITU) standard, ITU-T I.110 described in detail in T821 (1996). As such it should be standardised throughout Europe and possibly North America. The evaluation showed that the communications were 100% reliable. ISDN is being installed in many hospitals as part of the infrastructure for decentralised telemedicine where remote consultations can be undertaken by video link. Therefore, more ISDN lines should become available in the future. ISDN is more complex than courier but faster. It is more reliable than modems and again, faster.

In the initial definition of the aims of new technology in clinical research a fourth aim was given as the reduction in paper usage. This in our modern society is a highly relevant point. In the MRI spreadsheet system evaluation, it was calculated that almost 500 sheets of paper would have been required to collect just the image data from the six patients. It is not unknown for larger trials to use in excess of 500,000 sheets of paper during data collection with several such trials being required to complete a marketing approval submission.

6.3 Conclusions

The aims of this project were stated as: to fulfil the three aims stated initially for the implementation of new technology, be preferred over paper based collection systems and demonstrate the proof of concept of systems in the new paradigm.

To fulfil the three aims of new technology it is necessary to show a reduction in errors in the evaluated systems and an increase in processing speed when compared to the paper based process.

Table 6.1, *Summary performance measures for comparison*

Evaluation	Data entry or collection rate (dp/min)	Error rate per 10,000 data points
Clintrial	6.3	340
GUI Data Entry	8.9	160
Paper CRF	15.8	10-18e*
MRI Spreadsheet	35.1^	2.6

* Estimated figures from average CRF and DRF figures and Fritz (1997)
^ Figure includes one time data conversion and coding

Table 6.1 shows the performance comparisons for the evaluations where speed and error rates were measured. The MRI spreadsheet was clearly the fastest from the Sponsor's point of view and also produced the lowest error rate of all the technologies evaluated. Paper CRFs were next in speed. This point is highly relevant. The electronic CRF took 76% more time to complete than the equivalent paper CRF. Again, a systemic long term view must be taken to this apparent problem. Mirgoli (1996) and Lawton (1998) suggest selling the systems on the fact that the saving for the Investigator comes not from completing the CRFs but from not having to process DRFs later as a result of errors on the forms. More time is spent correcting errors after than correcting them first. Prevention is better than cure.

In order to show that new technology systems are preferred by the majority of users it is necessary to show statistically that more than half of all users, based on the results and sample size in all the evaluations, would say that the new technology systems were better. Table 6.2 summarises the results of the subjective preference measurement.

Table 6.2, *Summary of user preference measures for comparison*

Evaluation	Compared to	Number of responses	Better		Not Better	Unknown or not sure
GUI Data Entry	Clintrial 3.3	12	10	83%	2	-
MRI Spreadsheet	Paper CRF	2	2	100%	0	-
Adv. MRI spreadsheet	Paper CRF	3	2	66%	1	-
Video review for P002	Paper CRF	9	3	33%	3	3
Investigator questionnaire. Use of technology	Technology v Paper CRF	23	20	87%	3	-
Total		49	37	76%	9	3

Simple statistics of mean and confidence interval are used to compare preference results as suggested in Landauer (1988). The analysis of preference is only a broad indication but it suggests that most of the new technology was judged by the users themselves in real implementations as better than the current technologies. The 95% confidence interval on the figures for 'better' is ±22% therefore the average number of people who think that the new technology is better could

be expected to range from 54% to 98%. The result is sensitive to a small change in the two MRI spreadsheet figures. One less ‘better’ in either evaluation would result in the 95% confidence lower limit being under 50%. Small changes in the other results do not affect the overall indication.

Table 6.2 contains only preference measures for the technologies used for the collection of data and not the transport of data. The reason for this is that it is difficult to separate out the user preference for the ISDN from all the changes made in the trial in which ISDN was implemented. Transcripts of the user evaluations of the whole Imagine system are included in Appendix 8 and were generally favourable for the whole system.

Demonstrating that the concept of the new paradigm is proved is more complex. The design objectives of new paradigm systems were to reduce dynamic complexity and manage expectations. These were closely linked to the fundamentals of HCI, which were: understanding task, user and environmental factors. If the benefits of applying HCI principles have been realised by testing systems developed out of a paradigm evolved from these principles then it is fair to say that the new paradigm has a sound foundation at least. Some of the benefits of applying HCI were given as improved productivity, fewer errors, reduced costs and most importantly, improved user satisfaction. The project has succeeded in producing improvement in all these areas therefore can conclude that the new paradigm is a valid concept.

The new paradigm asserts that different technologies should be used in different situations as appropriate. Paper is appropriate where a computer is not appropriate because of environmental constraints or simply where completion will take longer for an already overworked Investigator. In this case, an entry system with an interface which produces efficient, low error rate data entry is important. It may also be appropriate to further investigate OMR/OCR for the collection of data in these situations. eCRFs are appropriate in situations where the time limiting factor is not the data entry but, as in the evaluation presented, the viewing of a video. Repetitive, high volume data types have been effectively captured into a spreadsheet. The capture of laboratory data and its transfer electronically is already a reality. Dynamic complexity has been reduced to detail complexity for each application of the technology and this will enable expectations to be more easily managed.

The systems evaluated in this project are only prototypes. The results are enough to demonstrate that there is a great need for continued development of better systems for the collection of clinical trial data and a greater understanding of Human Computer Interaction in the pharmaceutical industry. The business can save and the Investigators and other users want it. By considering the factors of good system usability from HCI and by using a genuine user participatory development method it is possible to develop these better systems.

6.4 The Future

The results from the open question in the Investigator survey and the comment from the MRI spreadsheet Investigator show that the Investigators recognise the benefits of the new paradigm. Their second highest concern in the survey was the ability to collect data more directly. More data providing equipment such as laboratory measuring devices, X-ray machines, MRI machines and ultrasound machines, ECG and EEG machines and many more are controlled by computer and can provide data directly to the data capture computer. Hyde (1998a) calls this Direct Data

Capture (DDC). This approach would remove much of the increasing duplication of data collection for the Investigator. The results of the image review questionnaire show that all centres where the Investigators worked store patient information on computers.

In the health care domain, there is an increase in computerisation of information with the capture of all patient information into an Electronic Patient Record (EPR). This EPR is a structured database containing much of the same information as required by the pharmaceutical industry. It would therefore be possible in the future to export the necessary information, as defined in the clinical trial protocol, to the Sponsor. This requires EPR and RDE system developers to begin a dialogue. Hyde (1998b) suggests that it is in both our interests and the patient's interest to identify synergies and work together for a better future. These advances really have the potential to fulfil the aims set out for new technologies like RDE. Errors should be reduced to nearly 0% and the resources required to transfer the data will be minimal.

The future is then to move away from the paper CRF paradigm and identify the types of data capture system appropriate for each data type and environment. This will lead naturally into the investigation of direct data capture options. Direct data capture is required to collect data into the electronic patient record systems otherwise hospitals will suffer the same problems as the pharmaceutical industry. Two industries working on the same problem with the common interest of patient care must find a way to co-operate for the sake of all involved.

GLOSSARY

AT Command set
A set of commands used to control the functions of modems.

Case Report Form or Case Record Form (CRF)
A CRF is a large and complicated questionnaire. It is the way that the Investigator provides the results of the examinations carried out with the Sponsor's product. Most CRFs are paper printed forms but see also eCRF.

Clinical Data Manager (CDM)
The Clinical Data Manager is a member of the Trial Team and is responsible for ensuring that the data is collected and that all the routines for Good Clinical Practice (GCP) in handling the data have been complied with. In co-operation with the statistician in the trial team the CDM is responsible for checking the quality of the data in the database.

Clinical Database
The database storage system for all the data collected in clinical trials where it can be archived, controlled and analysed.

Clinical R&D
The unit within a pharmaceutical company responsible for the management and running of clinical trials. The tasks of planning, performance and reporting are carried out in Clinical R&D. Overall product planning is done by the marketing department. Submission of ‘The File’ for marketing approval is done by Drug Regulatory Affairs (DRA).

Clinical Research Associate (CRA)
see Monitor

Clinical Research Co-ordinator (CRC)
The CRC is a specialist in the particular modality or application area of a new product. They are the trial designer and co-ordinator. One CRC is chosen to be the Trial Team Leader and has project management responsibility for the trial.

Contract Research Organisation (CRO)
A CRO is a service sector company that will run a contracted out trial from start to finish or any part of the trial.

Clinical Research Technician (CRT)
The CRT is responsible for the creation of the CRF, taking input from the CRC, statistician and the CDM. The CRT also often acts as a secretary. They are responsible for tracking the CRFs and the DRFs through the system.

Clinical Trial or Study
A clinical trial is a research experiment where a new drug or medical product is tried out in human subjects to see what its effect is. In contrast media trials it is usually to see of it produces an acceptable picture. Trials are often conducted to test methods, find suitable doses and examine the safety profile of the new drug.

Codelist
To ensure that the clinical database contains consistent information much of the data on a CRF is coded before or during data entry. The conversion lists are called codelists in Clintrial and other such applications. For example Male is coded to ‘M’ and Female coded to ‘F’.

Contrast Media
A contrast media is a substance administered to a patient by methods such as injection, infusion or orally so that when a picture is taken by one of the modalities such as x-ray or MRI particular parts of the picture are enhanced in order to make a better diagnosis of a patients condition.

Data Entry Application (DEA)
The DEA is sometimes called a multi-form. A DEA is made up of many individual data entry screens which are trial independent. The DEA groups these forms and inserts values into key fields for a specific trial.

Data Entry Instruction (DEI)
The information provided to the data entry staff explaining the special rules to be used in entering data from the CRF into the clinical database.

Data Request Form (DRF) or
Discrepancy Resolution Form (DRF)
A DRF is a form created when an error is located in the data that cannot be resolved without reference back to the Investigator.

Direct Data Capture (DDC)
The concept of capturing data electronically from medical, laboratory and other measuring devices directly into another computer for later transfer into the clinical database.

Double-entry
Data from the CRFs are entered twice by two different people and then afterwards a routine is run to compare the first entry and the second entry. Any discrepancies are printed to a log file. This is called blind verification. Verification of the second entry can also happen as the second enterer enters data. If there is a mismatch between first and second a warning appears and the enterer must choose which is correct. This is called heads-up verification.

Drug Regulatory Affairs (DRA)
The department responsible for contacts between the company and the regulatory authorities.

Electronic Case Report/Record form (eCRF)
An eCRF is the new type of CRF which is provided to the Investigator on a computer ready for direct entry of data. It will often have in built error checking and some functionality for the Investigator and Monitor to follow the progress of the trial and the patients.

Electronic Data Capture (EDC)
A generic term for the capture of clinical data by any of the common electronic methods such as RDE and RDE

Electronic Data Transfer (EDT)

The transfer of data between computers in electronic format normally directly over a communication link.

Electronic Patient Record (EPR)
A database which contains all relevant information about a patient. This can include amongst other information demographic information, drug and treatment information and images. The EPR makes patient information available to a doctor whenever and wherever it is required.

Electronic Standards for the Transfer of Regulatory Information (ESTRI)
A set of guidelines produced by the International Conference on Harmonisation (ICH) to govern the transfer of information used for regulatory submissions over the Internet.

File
The File is the collection of individual trial reports with an overall summary of the new drugs properties, effects and benefits that is sent to authorising bodies for approval to market the drug.

Food and Drug Administration (FDA)
The FDA is the government body in the USA which regulate the drug industry for the USA.

Good Clinical Practice (GCP) and
Good Manufacturing Practice (GMP)
GCP and GMP are the rules to which we must work when testing drugs on human populations to ensure the protection of the patient. They are being replaced by the recommendations from the International Conference on Harmonisation (ICH)

Graphical User Interface (GUI)
A computer display interface using graphical representations i.e. Microsoft Windows and Apple's Mackintosh, as opposed to text based displays such as DOS.

Human-Computer Interaction (HCI)
A discipline in computer science concerned with the design of computer systems described as "About understanding task, user and environmental factors in order to design systems that can be used effectively in the context in which they are placed" (PMT607, Unit 1, p.7).

Integrated Services Digital Network (ISDN)
A communication standard using digital as opposed to analogue transfer of information over a communication link.

Intelligent Character Recognition (ICR)
ICR is the latest type of OCR. OCR is the way that computers can recognise text printed on paper by scanning it and 'reading' it. However, OCR works only with printed text of a limited format. ICR can interpret handwriting. There are some limitations such as inter character spacing and all text must be in upper case.

Interactive Voice Response System (IVRS)
An IVRS system is a simple data collection system using a 'touch tone' telephone. When rung up the system plays a pre-defined sequence of questions that can be answered by pressing particular numbers on the telephone or by saying key words like 'now' or 'stop' to register a choice.

International Conference on Harmonisation (ICH)
These are a set of conferences between the US, European and Japanese drug regulatory authorities to try and work out a common standard of requirements for the submission of new drug applications. The conferences produce from time to time guidelines signed by all member countries. The guidelines are in accordance with and replace European GCP and GMP.

Investigator
The Investigator is a specialist doctor who is interested in research. S/he will accept to test the Sponsor's new product on his or her patients and record the results on the CRF. As a result the doctor will be able to publish the trials results with the Sponsor.

Magnetic Resonance Imaging (MRI)
MRI is a modality within medical imaging. An MRI machine is basically a large magnet. It can align the atoms in the different body cells in line with the magnetic field. When the magnetic field is removed the atoms will return to their original orientation. Depending on the type of tissue they will return to that orientation at different speeds. These speeds can be measured by a computer and displayed. MRI images are the sharpest images available.

Marketing Authorisation Application (MAA)
An MAA is the file and associated forms that are sent to authorities as a request for permission to market a new drug after clinical testing is complete

Master CRF
The CRF is the form used to collect data. Most trials are individually designed and require an individual CRF but many of the questions are the same on every CRF. The master CRF is the collection of questions that will always be the same for every trial.

Modality
A modality in clinical trials is the type of technology being used for the examination. These include x-ray, Magnetic Resonance Imaging and Ultrasound. The latest is Nuclear imaging.

Monitor
The Monitor or CRA as they are often called, has two roles. The first is to ensure that the trial centre and Investigators are carrying out the trial according to the protocol and that the CRFs are filled in to an acceptable level of quality. The also are the visible side of the sponsoring company and as such have an important customer relations role.
.

Multi-form
see Data Entry Application

New Chemical Entity (NCE)
The basic "ingredient" that will be refined and then tested to see if it has the potential to be turned into a new drug

Nycomed (Nycomed Amersham Imaging)
The company in which I am employed. A global market leader in the production of Contrast Media for diagnostic medicine.

Optical Mark Recognition (OMR) and

Optical Character Recognition (OCR)
The recognition of simple marks (OMR) or printed characters (OCR) in designated areas on forms specially designed to be electronically read and interpreted using a computer scanner and an appropriate application.

Principle Endpoint
A clinical trial can have several aims or endpoints but usually there is one that is more important. When all trial reports are combined into a File the principle endpoints together should complete the picture of the effects and benefits of the drug.

Protocol
The protocol is a document explaining all the details of the proposed trial. How it will be done, what products will be used, what type of patients will be recruited and how the results will be measured.

Remote data entry (RDE) or
Remote data collection (RDC)
These terms are used to describe the idea that the data for analysis is not entered at the sponsors central site but somewhere else remote from there. Normally this means at the Investigators site but can also be done at the Monitor's site. RDE uses an electronic CRF to collect data and RDC may use any form of technology such as phones (IVRS) or scanners (OCR).

SAS
SAS stands for Statistical Analysis System and is a program for statistically analysing large relational sets of figures. It has a large number of built in statistical analyses that just require the variables to be specified. SAS has its own special programming language.

Trial Team
The Trial Team is the group of staff that have responsibility for planning, running and reporting a clinical trial. It consists of a trial team leader who is normally a CRC, maybe an extra clinical research co-ordinator, a statistician, a Clinical Data Manager, a secretary and often a clinical research technician.

Trial Team Leader (TTL)
The leader of the Trial Team. A kind of project leader role. Usually a senior Clinical Research Co-ordinator.

World Health Organisation (WHO)
An International body that co-ordinates health matters on a global basis especially in a pharmaceutical context, the naming of drugs and the side effects of such drugs.

APPENDICES

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Tables

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Appendix 1. User Comments and Observation of Clintrial 3.3

Summary of recent internal questionnaires and surveys of data management staff

- Two or more items from one record in a Clintrial panel can not be entered from more than one entry screen (form). The example is demographic information gathered from more than one CRF page
- Wide records will not print completely. The problem occurs when writing the print file.
- It is not possible to go back to for instance previous patient during entry if you want something or realise that you have just made a mistake. Entry personnel have said that it would be convenient as an alternative to get some sort of warning that the page is about to shift
- If a codelist is used for numerous trials, it is not possible to filter out only the appropriate codes when entering data for one particular trial
- Each form can only be used to enter data into one panel
- Screen editor is not perceived as good
- Multiform editor is not perceived as good
- Screen layout does not resemble CRF layout very well
- No cut and past facility to repeat typed information when creating entry screens
- Cannot modify existing form specification, must re-enter all details
- Can't use codelists when filling in occurrence values
- Highlights not fully available on the entry screens therefore written instructions are needed that are not read
- No flag to say that a record has not passed validation so all records must be validated all the time
- Errorlogs are protocol specific and are therefore written over if someone else validates a panel afterwards
- Requirement to create a trigger to trigger a SAS program after a Clintrial validation is finished

Clintrial Problems identified from informal observation

- Codelist field length on screen not long enough to see whole code
- Codelist items are not predictable so must be looked up or often guess wrong and different codes are used for the same item in different codelists
    - Normal = NORM, NORMAL, N,1,10,210,1000
    - Other = O, OT, OTH, OTHER, 999, 9999
    - Post Operative = PO, POSTOP
- Punctuation causes most verify errors with text strings, space or not space
- Multi record non-tabular forms i.e. AE form cause problems if next record is hit by mistake, record disappears
- "Where am I on a form in relation to the screen" is a question often asked
- Laboratory values entry screen is nothing like the paper reports. The word usage is completely different and causes very slow data entry
- Physical/ergonomic problems after entering one form for one hour
- Must tab. through all fields even if some are not applicable as there is no go to field type functions
- Cursor movement problems on sides like medication
- Enterers try to remember codes instead of looking them up

- Entry staff do not read the screen where codes are written on the screen if intuition says otherwise
- Codes from codelists written on screen speed up entry
- Some CRFs take four days to learn to be able to enter unsupervised.
- Entry staff guess codes for items with no exact match.
- Before employing entry staff check their typing skills
- Some forms have taken 50% longer to enter, suspect distraction. No pressure on work
- The fact that the first form of the day, especially the first of the day on a Monday morning, takes longer to enter can show a strong learning/forgetting effect. T016 also showed that clearly. Entry was in batches and each enterer thought they remembered how to enter things and didn’t
- Looking up in codelists can take longer if codelists are too big. (Suggest limited codelists)
- Different instructions for standard items such as medication dose/freq. and use of , or . for numbers cause cross over learning effects

Appendix 2. Results of Heuristic Analysis on Clintrial 3.3 User Interface

Table A2.1, *Heuristic analysis of Clintrial 3.3*

Evaluator Category	Ev#1	Ev#2	Ev#3	Ev#4	Ev#5
1 Dialogue	n	U	y	n	n
2 User Language	y	Y	y	y	y
3 Consistent	n	Y	y	y	y
4 Feedback	n	N	n	n	n
5 Exits	n	n	n	n	n
6 Shortcuts	n	n	n	n	n
7 Error messages	n	n	n	n	n
8 Help visible	n	n	n	n	n
9 Intuitive	n	u	n	n	n

y = yes, n = no, u = not sure

Appendix 3. Summary of Extra Information Written onto CRFs Where No Space Provided

100 CRFs were checked. 5 forms for each of 20 Investigators. Table A3.1 below shows a summary of the findings.

Table A3.1, *Summary of Investigators providing extra information*

Investigator	CRF 1	CRF 2	CRF 3	CRF 4	CRF 5
Inv#1	-	x	-	-	-
Inv#2	x	-	x	x	X
Inv#3	-	-	-	-	-
Inv#4	-	-	-	-	-
Inv#5	-	-	-	-	-
Inv#6	x	-	-	x	x
Inv#7	-	-	-	-	-
Inv#8	-	-	-	-	-
Inv#9	-	-	-	-	-
Inv#10	-	-	-	-	-
Inv#11	-	-	-	-	-
Inv#12	-	-	-	-	-
Inv#13	-	-	-	-	-
Inv#14	-	-	-	-	-
Inv#15	x	-	x	-	-
Inv#16	-	-	-	-	-
Inv#17	-	-	-	-	-
Inv#18	x	x	-	x	x
Inv#19	-	-	-	-	-
Inv#20	-	-	-	-	-

x = additional information entered

Appendix 4. Simulated CRF Completion Times

The Master CRF was completed 10 times by several different people to simulate the manual collection of information onto a paper CRF.

Table A4.1, *Simulated manual CRF completion times*

Simulation no.	Time (min)
CRF #1	7.2
CRF #2	6.5
CRF #3	6.8
CRF #4	6.8
CRF #5	7.0
CRF #6	6.4
CRF #7	6.6
CRF #8	6.7
CRF #9	7.4
CRF #10	6.8
Average	6.8

Appendix 5. Batch Error Rates for Clintrial Data Entry - Real Trials

V056, 21 patients, 158 errors out of 1144 records = 14%
V056, 4 patients , 88 errors out of 214 records = 41%
V056, 10 patients, 114 errors out of 643 records = 17%.
V056, 10 patients, 137 errors out of 674 records = 20%.
V056, 10 patients, 127 errors out of 668 records = 19%.
V056, 10 patients, 45 errors, 683 records = 7%.
V056, 10 patients, 32 errors, 825 records = 4%.
V056, 6 patients, 68 errors, 415 records = 16.4%
V056, 20 patients, 45 errors, 1523 records = 3%
V056, 30 patients, 39 errors, 2020 records = 2%.
V056, 27 patients, 53 errors, 1764 records = 3%

V055, 20 patients, 18 errors, 918 records = 2%
V055, 9 patients, 21 errors, 484 records = 4%
V055, 17 patients, 48 errors, 887 records = 5%
V055, 19 patients, 27 errors, 981 records = 3%
V055, 27 patients, 130 errors, 1394 records = 9%
V055, 31 patients, 306 errors, 1702 records = 18%

V051, 102 patients, 545 errors, 5067 records = 11%
V051, 177 patients, 616 errors, 8865 records = 7%
V051, 40 patients, 174 errors, 2052 records = 8.5%

V050, 33 patients, 215 errors, 1649 records = 13%
V050, 21 patients, 113 errors, 1073 records = 11%
V050, 28 patients, 61 errors, 1355 records = 5%
V050, 15 patients, 44 errors, 759 records = 6%
V050, 26 patients, 38 errors, 1180 records = 3%
V050, 39 patients, 254 errors, 1691 records = 15%
V050, 50 patients, 75 errors, 1844 records = 4%
V050, 60 patients, 86 errors, 2833 records = 3%
V050, 15 patients, 23 errors, 731 records = 3%
V050, 21 patients, 55 errors, 964 records = 6%

T006, 2 patients (test), 60 errors, 485 records = 12% error rate

T017, 1 patient, 105 errors, 265 records = 40%
T017, 1 patient, 53 errors, 254 records = 21%
T017, 5 patients, 160 errors, 1147 records = 14%
T017, 9 patients, 28 errors, 1855 records = 1.5%

T018, 13 patients, 23 errors, 959 records = 2%
T018, 1 patient (test), 13 errors, 90 records = 14%

Appendix 6. Master CRF Evaluations Test Data Set

Demographic: *Date of birth*, 07/10/1964; *Patient Initials*, AHY; *Visit date*, 18/04/1997; *Sex*, Male; *Race*, Caucasian; *Weight*, 64 kg; *Height*, 174 cm; *Comments*, None.
Medical indication: *Vertigo*, No; *Symptoms of congestive hear failure*, Yes; *Suspected foreign body*, No; *Leakage suspected*, Yes; *Other*, None; *Comments*, None.
Other relevant medical history: *Diabetes*, No; *Asthma*, No; *Hay fever*, Yes; *Known hypersensitivity to any drug*, Yes; *Specification*, Allergic to penicillin; *Comments*, None.
Routine and non related medication (conco meds): *Medication taken*, Yes; 1; Aspirin, 10mg, 4x1, po., knee disorder; 2; Myotoxinol, 1mg, 4l/d, po, constant tiredness; 3; Cardinodimal, 10ug, 1c/h, iv., iron deficiency; Binatriumberate, 10g, 1cap/w, nas, headache; 5; Carrot juice, 1 glass, 1g/d, po, to see in the dark better; *comment*, None.
Pre medication: *Medication taken*, Yes; 1; Ferronexate, 1mg, 18/04, 12:00, td, extreme nervousness; 2; Talcum powder, 10g, 18/04, 12:05, td, extreme perspiration; *comment*, None.
Medication during examination: *Medication taken*, No.
Post medication: *Medication taken*, Yes; 1; Baileys Irish Cream, 1 glass, 18/04, 15:00, po, patient needed a drink; *comment*, The post examination medication is not recommended for unhealthy volunteers.
Adverse events: *Were any adverse events observed*, Yes;
1; *Kind of event*, Feeling of thirst; *Onset*, 14:50, 18/04; *date reported*, 18/04; *duration*, 00:10:00; *Present before drug admin*, No; *Related to the trial drug*, Uncertain; *If none or Uncertain*, Unknown; *Severity*, Moderate; *Discomfort*, Yes; *Serious AE*, No; *Action taken*, Medical treatment; *Outcome*, Recovered; *Comments*, Medication given filled out on AE page
2; *Kind of event*, Tiredness; *Onset*, 19:50, 18/04; *date reported*, 18/04; *duration*, 15:00:00; *Present before drug admin*, Yes; *Related to the trial drug*, No; *If none or Uncertain*, Medication; *Severity*, Severe; *Discomfort*, Yes; *Serious AE*, No; *Action taken*, No action required; *Outcome*, Remaining sequela; *Comments*, None.
Final page: *Were all inc. criteria fulfilled*, Yes; *Was the patient withdrawn*, No; *Comments*, None.

Appendix 7. Observations of GUI Interface Problems

Demographic

The CRF does not state anywhere whether the patient to be entered is a pilot patient or not. Entry personnel is expected to enter something which is not on the CRF. *(Category - Alignment)*

Even though the data format to be entered is specified in the help text on the entry screen, the format does not match the data format on the CRF. Entry personnel is expected to enter the date in a different format than what they read on the CRF. *(Category - Alignment)*

Visit

Demographic and visit information is recorded in the same section of the CRF, while the entry is to be performed through two separate entry screens. The CRF is not designed with this in mind. Entry would be considerably more intuitive if the information in this section of the CRF was grouped and sequenced according to the sequence of entry (visit date close to the end and grouped with weight and height), which it is currently not. *(Category - Alignment)*

Weight and height are interchanged on screen. *(Category - Alignment)*

No reference anywhere as to where comments are to be entered. Presumably it is on the comments screen. *(Category - Better Help)*

Indication

Indication number on the screen has no reference on the CRF. Entry personnel is expected to enter something which is not on the CRF. It is not explained anywhere whether the indication number is supposed to be related to the suggested indications listed on the CRF, or whether they are supposed to be related to the indications actually present. *(Category - Alignment)*

No reference anywhere as to where comments are to be entered. Presumably it is on the comments screen. *(Category - Better Help)*

Medical history

There is nowhere on the screen the information in the "none" box on the CRF can be entered. *(Category - Alignment)*

The entry screen does not specify in the lead text that it expects a Y/N answer. Entry personnel have to guess on the basis of the CRF, or by displaying the codelist. *(Category - Better Help)*

The "Other" option in the list of illnesses does not have a Yes box & a No box like all the other options. Entry personnel have to guess where and how this design inconsistency affects the entry. *(Category - Alignment)*

Entry personnel have now become accustomed to entering comments from the CRF into the comment screen. Suddenly "comments" outside each listed illness in the CRF is supposed to be

entered in an entry field called "specification" on the medical history screen. *(Category - Inconsistency)*

No reference anywhere as to where general comments are to be entered. Presumably it is on the comments screen. *(Category - Better Help)*

Concomitant Medication

The Y/N field on the beginning of the field indicates from previous experience a "Yes" box & a "No" box on the CRF. In stead, this time it relates to one single "None" box. Entry personnel have to guess and enter something different from what is on the CRF. *(Category - Alignment)*

Whether it is routine medication or not can only be entered for the first medication on the list despite the fact that it is recorded on the CRF for each one individually. *(Category - Alignment)*

Which code to use in the time field is unclear. Entry personnel have to guess that it relates to the "within 24 hours" statement in the CRF heading and further guess whether this relates to the "-24" or "-24-0H" code. Entry personnel have to guess and enter something different from what is on the CRF. *(Category - Alignment)*

The Routine Med. Y/N field on the screen does not relate to a "Yes" & "No" box in the CRF. The corresponding negative phrasing in the CRF makes it even more difficult to get it right. *(Category - Alignment)*

Pre medication

The Y/N field on the beginning of the field indicates from previous experience a "Yes" box & a "No" box on the CRF. In stead, this time it relates to one single "None" box. Entry personnel have to guess and enter something different from what is on the CRF. *(Category - Alignment)*

Date given can actually be entered "EXACTLY as written on CRF" (1804), as stated in the entry instructions. That is good, but not consistent with previous experiences of having to enter the date in a specific date format. *(Category - Inconsistency)*

Time given on the other hand can not be entered "EXACTLY as written on CRF". It requires a special time format which is not displayed neither on the CRF (which would be preferable) nor on the entry screen. *(Category - Better Help)*

During medication

The Y/N field on the beginning of the field indicates from previous experience a "Yes" box & a "No" box on the CRF. In stead, this time it relates to one single "None" box. Entry personnel have to guess and enter something different from what is on the CRF. *(Category - Alignment)*

Even though no medication is given, the "No:" field in the entry screen is mandatory and a number has to be entered as if medication was given, which does not make much sense to the entry personnel. *(Category - Illogical)*

After medication

The Y/N field on the beginning of the field indicates from previous experience a "Yes" box & a "No" box on the CRF. In stead, this time it relates to one single "None" box. Entry personnel have to guess and enter something different from what is on the CRF. *(Category - Alignment)*

Date given can actually be entered "EXACTLY as written on CRF" (1804), as stated in the entry instructions. That is good, but not consistent with previous experiences of having to enter the date in a specific date format. *(Category - Inconsistency)*

Time given on the other hand can not be entered "EXACTLY as written on CRF". It requires a special time format which is not displayed neither on the CRF (which would be preferable) nor on the entry screen. *(Category - Better Help)*

Adverse Event

Where is follow up check supposed to be entered? *(Category - Alignment)*

The "Event present" field in the entry screen does not comply wit any of the lead texts in the CRF. Entry personnel have to guess what to enter. *(Category - Alignment)*

The "AE no:" field in the entry screen does not comply wit any of the lead texts in the CRF. Entry personnel have to guess what to enter. *(Category - Alignment)*

The "Event as reported:" field in the entry screen does not comply wit any of the lead texts in the CRF. Entry personnel have to guess what to enter. *(Category - Alignment)*

"Report date:" has not identical lead text wording in the CRF and the entry screen. Entry personnel have to guess. *(Category - Alignment)*

"Report date:" comes before onset in the entry screen and behind onset in the CRF. *(Category - Alignment)*

Time and date formats required during entry for all date and time items, are not described neither in the CRF, the entry instructions nor the entry screen. *(Category - Better Help)*

The layout of Yes/No entry fields is not consistent across entry screens, nor even within the AE screen. *(Category - Inconsistency)*

The values to be entered from seemingly similar codelists (Cause and Severity) next to each other are not consistent. One is a logical letter abbreviation. The other is just an illogical number. *(Category - Inconsistency)*

Items in the entry screen and CRF's are not grouped the same way (column wise on the CRF, row wise on the entry screen). *(Category - Alignment)*

"Event present:" is not on the CRF for the second event. It has already been entered for the first one, and entry personnel have to guess that it is to be entered once more. *(Category - Alignment)*

Comments

The item kind_of_com code should be printed on the CRF. Entry personnel now have to browse through the codelist and guess which one it is. *(Category - Better Help)*

Adverse event comments. Suddenly the comment is not to be entered in the comment screen, but rather in a field on the AE screen. *(Category - Better Help)*

Appendix 8. User Comments on the 'Imagine' System for Scanning and CRF Transport.

- It was a good experience and, personally, I appreciated very much. Much more than the self-copying CRFs!

- Of course it is time consuming to scan and then mail the CRFs. But if the equipment is placed close to the place where it is possible to verify/monitor the following CRFs, it is possible to organise in order to do both simultaneously. The location of the equipment is very important! Also you should be ready to stay at the centre for long days , or more days, when there are many CRFs to send. This was however due to the fact that we had to wait for the lab results which arrived with much delays and therefore we could not scan from the first visits.....

- The use of the system was for me well monitor's friendly and even me who are not good in using PCs was able to use it. The preparation of the tables and the reports was a good help. However I think we can improve it (the lay out) for the Phase III.

- The reception of DRFs and the response to them was very easy (after the printing problems were solved!), and rapid. This is a real advantage.

- According to me, seen from the monitor's point of view, I think the total handling of the CRFs/DRFs is with this system of scanning and mailing faster than any other system already used. May be the CRFs could be on self copying paper so we do not have to take copies for the centres and ourselves at the end. (The copies scanned and stored on the disc are difficult to read and we had to delete some of them to restore space on the disc).

- Support from you in Oslo was OK for the practical part. The telephone contacts not being always very easy or good but this is a tel communication problem.

- OK for me to continue for Phase III

- I was surprised to have made good experience with our new system of transferring data.

- Scanning was not time consuming, but transfer of data from Paper Port to Group Wise.

- My biggest problem was to not have in each centre an ISDN line. That means, messages haven't reached me at the centre Aachen (for example), but one day later at Cologne and had to wait to be completed/added/corrected for a whole week, until my next visit at the centre Aachen.

- Support from Oslo was great. I would like to say many thanks for it. When needing help during the work at the centres (scanning and data transfer) I could call anybody (mostly Tore) to ask for. Only once, nearly in the end of the scanning work nobody could help ...

- It's a pleasure to use a system like this but only in centres which have an own ISDN-line, to get immediately comments etc. for discussion. ... For centres not having an own ISDN-line unfortunately it isn't a really time saving system. Copies or telefax would do it also.

The comments above were received by e-mail from the Monitors and the use of English has not been changed.

Appendix 9. Master CRF Entry Speed Measurements and Preference Results

Table A9.1, *Clintrial and GUI Data Entry - Entry Times*

User	Data Entry user	Time with Clintrial 3.3 (minutes)	Time with Windows GUI (minutes)	Clintrial general use	Subjective preference comparison
Ev#1	yes	13	11	Regular	Better
Ev#2	yes	14	-	Regular	-
Ev#3	no	Did not complete	17	Ex	Better
Ev#4	no	23e	12	Ex	Better
Ev#5	no	24	-	Seldom	-
Ev#6	yes	14	10	Regular	Better
Ev#7	yes	15	-	Regular	-
Ev#8	no	20	-	Seldom	-
Ev#9	yes	15	-	Regular	-
Ev#10	yes	13	-	Regular	-
Ev#11	yes	14	-	Regular	-
Ev#12	yes	13 13	8 8	Seldom	Better
Ev#13	no	22	15	Never	Better
Ev#14	no	21	-	Seldom	-
Ev#15	no	21	14	Never	Better
Ev#16	yes	18	-	Regular	-
Ev#17	yes	18	18	Regular	The same
Ev#18	yes	13	12	Regular	Worse
Ev#19	no	-	17	Supervisory	-
Ev#20	yes	-	11	Regular	Better+
Ev#21	yes	-	11	Regular	Better+
Ev#22	no	-	15	Ex	Better+
Average		17	13		

e - estimated due to too many interruptions

+ - Comparison based on general use of Clintrial not Master CRF entry

Appendix 10. E-mail from the MRI Spreadsheet Investigator

The following text is taken from an e-mail I had sent to the Investigator who used the MRI spreadsheet :-

Dear Dr Wang,

I was the creator of the spreadsheet and I would like to add my thanks to you for filling it out in the way you did. We have now transferred the data into the database and the experiment looks to have succeeded.

There was a lot of data!! 4602 signal intensity measurements in total. (I hope that agrees with what you think!!)

Now we have finished I would like to ask you what you thought of this way of collecting the signal intensity data. I am writing a Masters Degree dissertation on the subject of new technology methods of capturing clinical data and your experiences would be very useful for me. Both negative and positive.

Did you like the system?
Did it function correctly (I.e. did the machine crash)?
Was it easy to use?
Was it quicker than paper?
Was it better than paper?
Would you do it like that again if asked?
Have you used other electronic data capture systems before?
Was this better or worse than any other systems?
Was it intuitive to use?
Was it difficult to learn to use?
Did it fit in with your routines for measuring SI?
Any other comments at all on the system??

Lots of questions but I hope you can find time to answer most of them.

Thank you again for your co-operation with this new system.

Andy Hyde
Clinical Systems Developer.

The Investigator's reply is as follows :-

Dear Andy,

In general the system worked fine. There is no crash during its operation. The computer was relatively slow as it has a slow processor. It can be said easy to use. I had not much experience in using Excel spreadsheet before, but it took me no time to understand and know how to use it.

Again, the portable computer made it difficult to input digital figures because of the keyboard design. But this is not your fault and I think it's still faster and better than writing on a paper first, then type them into the computer. The latter way can double the chances of typing mistakes to say the least, and therefore is not a method of choice.

I usually use a statistical program (Statview, or JMP for Macintosh) directly for data input. They are basically the same for me to use for the purpose of typing in values, but it is easier to do preliminary statistical analysis with statistical programs to see trends at the middle of measurements. I guess Excel may be better if used as a platform for larger data bases.

At last, I wish that you can design a program that is able to transfer ROI measurements from MR computer to a portable computer electronically. Only that can ensure the fastest and error-free data input.

Good luck with your project!

Appendix 11. P002 Investigators Meeting - Electronic Data Capture Questionnaire

Centre name _____

As a way to estimate the potential use of Electronic Data Capture by Nycomed we would be pleased if you would answer a few questions about how you view this new technology.

Please put a cross in the appropriate box.

	Agree or Yes	Do not agree or No	Not sure or don't know
1) This method of capturing data is appropriate for blinded reads			
2) This method of collecting data can be used for any type of data			
3) This method of collecting data is better than using paper			
4) Computers will replace paper forms completely for clinical trials one day			
5) I use a computer every day for my work			
6) The place where I work stores patient or examination records on a computer			
7) The data capture solution for the P002 was a good solution for the trial			

Any other comments about electronic data capture.

_____

_____

_____

Figure A11.1, *Questionnaire for the Video Review meeting*

Appendix 12. Investigator Survey Questionnaire and Results

"New Technology Being Tried in the Collection of Clinical Trials Data in the Pharmaceutical Industry - An HCI comparison

Investigator survey

The Open University

	YES	NO
Your use of computer technology in Clinical Trials		
1) Have you ever used computer technology, a computer system or a computer application for the collection of data in a clinical trial?	○	○
If YES please answer the following questions. If NO please go to question 6.		
2) Did you consider the technology, system or application usable (User friendly)?	○	○
3) Did you think that the technology, system or application was especially suitable for its intended purpose?	○	○
4) Did you like using the technology, system or application?	○	○
5) Would you consider using the same again?	○	○
Your view of the future.		
6) Do you think that computer technology for collecting clinical data is better (if you have experience), or would be better (if you have never used any), than using paper?	○	○
7) If you think that computer technology will one day replace paper for collecting clinical data, approximately what year do you think this might happen?	_____	

8) Is there anything you as an Investigator would like from a system based on computer technology so that you would benefit from using it? (Please continue on the reverse if necessary)

Andy Hyde

AandR\invsurv.ifd

Figure A12.1, *Investigator survey questionnaire*

Responses to the final open ended question of the questionnaire

- A user friendly system which can be handled by all patients in a clinical study. The system must be 100% secure and easy to tap to other computer systems.

- The question is unclear. I have used computer technology to collect data into a database not directly without paper. For the doctor it is less time consuming to do the paperwork. Monitoring is still necessary, teaching, supervising and discussing and most important motivation is all underestimated and cannot be replaced by a computer. There is very little cost-benefit if data supposed to be controlled are verified.

- Avoiding paper work and large files with data

- Ease and quickness of entering data into the computer, preferably by scanning documents or by voice activated methods.

- Ability to detect “Abnormal data” (too low or too high) = already possible.
- Interactive system that takes care of corrections and explanations.

- On line calculations

- Simplification of data input, import data base into commercially available programs, (Excel, Word etc)

- - Easy to use
- - Real time transmission of data
- - Real time transmission of questions about the study
- - The most important problem is the security of the problem regarding the patient and the laboratory

- Easy to use
- Connectivity/networking/pull and push data

- Laptops that will be small, have low weight that can be used when seeing your patients in the clinic and elsewhere.

- Problems
- - The data entry form must be PERFECT!
- - Lack of compliance/co-operation of some clinical Investigators
- Best regards

- A system based on computer technology should be extremely easy to use, portable (palmtop) and have the possibility to be adapted to serve a certain purpose

- It should be very easy to gather information from several other sources and to combine them in order to save time wasted on entering the same data several times.

- It should be capable of giving overviews and results fast and in definable formats.

- Simple and not too time consuming

- A lot of work would need to be done to ensure that systems interface with equipment on site at trial centres.

- I used computers for small clinical studies as a tool for database + statistics + graphics (usually Excel) but never in the form of a CRF.

- CRFs are a real pain and a computer may make it much easier and friendly.

- Note: I have never used computer technology to collect data in a trial sponsored by a pharmaceutical company.

- My own hand-held organiser (Psion 3a) is extremely useful for data collection - I design my own spreadsheet + then upload onto the desktop.

- - to shorten time
- - to simplify daily work
- - to archive data
- - to process data

- I think error checking software is critical
- It must be highly mobile. A pen-screen interface could be useful. Should be able to store some recordings directly (ECG).

- Ease of application
- Memory power
- Able to carry out complex statistical analysis"

- User friendly

- Clinicians are busy. An unfriendly system is never good.

- Needs the companies who sponsor studies to try it out.

- All answers should be 'fool proof' so that you always fill everything out (no blanks and a 'ping' question every time an answer is out of range or unreasonable

- Ease of use and Reliability

- Easy to use format. Windows/graphical orientated user interface
- intelligent data management

- Quick data input
- user friendly interface

- easy to input
- user friendly
- versatile with statistics built in

Appendix 13. Financial Justifications and Assumptions

The following table assumes a trial with 150 patients.

Table A13.1, *Examples of potential cost savings from the use of new technology*

Metric	Normal	New	Normal cost	New cost	Resource saving	Opportunity cost
CRF design	15 days	3 days	£3,500[1)]	£750	£2,750	(12 days)[5)]
Data queries	750[4)]	150	£2,250[2)]	£450	£1,800	
DRFs	75[4)]	15	£1,350[2)]	£270	£1,080	
Site visits	10	5	£7,000[3)]	£3,500	£3,500	
Data entry	67 days	0 days	£16,750[1)]	£0	£16,750	(33 days)[7)]
Database locked	177[6)]	2	£12,500[1)]	£500	£12,000	175 days
Database locked (Compared to fastest trial)	*21*	*2*	*£5,250[1)]*	*£500*	*£4,750*	*19 days*
Totals			£43,350	£5,470	£37,880	175 days

1) at an FTE (Full Time Employee) cost of £250/day (2500kr/day Norwegian FTE at 10kr = £1, approx.)
2) at a cost of £3 per query, £18 per DRF and 10% DRF rate on queries. (Based on FTE cost)
3) at an estimated site visit cost of £700 ($1000)
4) there are an average of 150 patients per trial
5) if CRF design is on the critical path then is a further 12 day opportunity cost saving.
6) the average number of days to lock the database is 177 days. An estimate of 50 of those days are actual resource used.
7) data entry is very often done after the last patient has been included in the trial making it a critical path activity therefore there could be an opportunity cost saving

The savings above do not represent a cost/benefit calculation because the cost of the technology itself and the labour to set it up and maintain it have not been taken into account.

Assumptions made for these calculations

1. In Phase II & III trials since 1990 there have been an average of 150 patients per trial enrolled
2. From analysis of the number of errors per trial based on records per trial there are 55 records per patient on average. (50913 records in 919 patients.)
3. At 55 records per patient and 5.7 data points per record there are estimated to be 313 data points per patient CRF. For 150 patients this is 46,950 data points per trial
4. At a data entry rate of 6.3 data points per minute this would take an average of 49 minutes to enter. All CRFs are double entered so this is a resource use of 98 minutes.
5. records per patient at 7.9% error rate average = 668 errors per trial.
6. per day FTE includes wages and overheads to keep the person employed.
7. At £250 day and at 5.2 minutes per query each query costs £3. Each DRF takes 30 minutes to create and therefore costs £18.
8. The average time to lock a database in trials where the last patient was included after 1/10/94, approximating with a re-organisation in Clinical R&D, was 177 days.

The savings of £37,880 do not take account of any costs of new technology. The roughly estimated costs for a ten centre European trial lasting 6 months could be :-

Equipment	10 x £2,000	£20,000
One FTE		£15,000
Installation costs (travel)	10 x £500	£5,000
Depreciation at 30% p.a.		£3,000
Communications links and call charges		£2,000
		======
		£45,000 minimum

Cost per patient of different data collection technologies

For a 200 patient trial with ten centres lasting six months and a 20 page CRF, 4000 individual forms are produced.

Current methods would cost an estimated 2 FTEs for six months supervising data entry and correcting errors and creating DEAs = £60,000. An estimated 80 man days would be required to manually enter the data. (based on 21 dp/page, 6.3 dp/min, 5.5 hrs/day, double entry, £30 per hour professional data entry staff rate) = £13,200. Total = £73,200. £366 per patient.

RDE would require at least £45,000 in equipment costs for ten centres (see earlier calculation in this appendix). But at least 0.75 FTE CDM for six months would not be required as the quality of returned data is much higher = - £22,500. Total = £22500. £112.50 per patient. There is also a big assumption that the Investigator is not paid extra for using RDE, the benefit to him/her is a reduction in DRFs that are quite time consuming. Table A10.2 shows rough costs estimations per centre for the use of RDE.

Table A13.2, *Costs of RDE per number of centres*

Number of Centres	Equipment costs	labour for maintenance	Install-ation costs	depre-ciation	call charges	-CDM	Total	Per patient
1	2000	1500	500	300	200	-22500	-18000	
2	4000	3000	1000	600	400	-22500	-13500	
3	6000	4500	1500	900	600	-22500	-9000	
4	8000	6000	2000	1200	800	-22500	-4500	
5	10000	7500	2500	1500	1000	-22500	0	
6	12000	9000	3000	1800	1200	-22500	4500	22.50
7	14000	10500	3500	2100	1400	-22500	9000	45.00
10	20000	15000	5000	3000	2000	-22500	22500	112.50
15	30000	22500	7500	4500	3000	-22500	45000	225.00
20	40000	30000	10000	6000	4000	-22500	67500	337.50

* All figures are in GBP

OCR scanned forms would take 66 hours or 12 days (based on 5.5 hrs/day) to check and correct having been scanned unattended = £1980. A scanner and the software cost a maximum of £500. Total cost £3500. £12.40 per patient.

Taken out of the equation is 1 FTE for six month for creating the CRF and correcting errors that are not a factor of the technology.

One FTE is calculated at £250 per day.
dp = data points

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