

Internet-Based Clinical Trials

Practical Considerations

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Abstract

Internet-based clinical trials (IBCTs) are rapidly changing the current paradigms of clinical research, data management, statistical analyses, medical writing, and even regulatory submissions and reviews. Competitive forces are driving the implementation of IBCTs in that they provide cost-effective solutions for streamlining areas such as patient enrollment, data entry, query management, communications, regulatory review, and project

management. By reducing data entry errors through the use of online edit and logic checks, there is improved data quality as well as a reduction in the time to database lock.

Company-sponsored clinical research has always had project management as an important component. By providing online reports directly from the database, IBCTs significantly improve the project management aspects of clinical research and reduce or even eliminate many project management expenses. Within 2 years, by necessity, sponsored clinical research will use some form of Internet-based system to assist in the conduct of clinical trials. This will occur as: (i) the prices for Internet-based systems fall with more competition; (ii) there is increasing confidence in the use of electronic data; and (iii) economies of scale develop as studies with similar designs, architectures, and business rules are implemented.

Benefits, structural changes, examples of cost savings, practical recommendations for program implementation, and selected metrics (measurements of system performance) are presented. While the benefits for IBCTs are in the areas of randomized controlled trials, postmarketing studies, patient registry studies, and project and safety management, this article focuses on randomized controlled trials. This article is based on IBCT experience in the US, Europe, and the Middle East.

Internet-based clinical trials (IBCTs) are radically changing clinical research, data management, statistical analyses, medical writing, and even regulatory submissions and reviews. IBCT solutions offer a convenient, cost-effective approach for streamlining areas such as patient enrollment, data entry, query management, communications, regulatory review, and project management. By reducing data entry errors through the use of online edit and logic checks, there is improved data quality as well as a reduction in the time to database lock, the time at which data are no longer entered into the database. Thus, companies can reduce both the time to market and costs.

However, the transition from the world of paper Case Report Forms (CRFs) to the paperless world of IBCTs is fraught with many obstacles. The obstacles are human-based, not technical, and most are avoidable when good-quality practices are established. The main obstacle from a practical perspective is the lack of experience most managers have in IBCTs. Inexperienced managers often demand more features from the system than are needed, resulting in user-unfriendly and unnecessarily complex electronic data capture (EDC) systems. When this happens, all team members are frustrated, management is upset, and the initial goal of replacing paper CRFs is not achieved.

In the 1980s, with the introduction of the personal computer, pharmaceutical companies began to experiment with a concept called remote data entry (RDE). When RDE was implemented, a company would provide a computer to a clinical site. The clinical site would collect data in paper source documents, then enter these data into computer-generated data entry screens. The computerized data were then usually returned to the sponsor on a floppy disk via an overnight delivery service. These tasks would occur repeatedly during the course of the clinical trial. Data lock would

occur after completion of source document verification by the study monitors.

In 1997, a report was published regarding the Internet and randomized controlled trials.^[1] The authors addressed the factors that could constrain the implementation of IBCTs. The authors also addressed the advantages of using IBCTs to obtain large sample sizes with reduced unit costs through global access, fast interaction, and automation. In 2001, an article addressing the use of Internet technologies for data acquisition in clinical trials supported the premise that IBCTs provide a fast and easy avenue for the acquisition of scientific data.^[2] The article predicted that this method of data acquisition and data processing will become more common in multicenter clinical trials. In 2003, a detailed article was published on planning and running an IBCT.^[3] The article addressed the issue that IBCTs will revolutionize the clinical trial process and supported the concept that prior to implementation, all team members must identify and review all of the necessary elements of the program.

Now that the Internet has provided the ability to perform data entry by any authorized user who has a computer with Internet connectivity (e.g. dial-up, broad-band) and a web browser, there is no longer a need to go through the laborious processes of data entry from paper CRFs, or even classical RDE. RDE has now evolved into Internet-based RDE (I-RDE), which is also called EDC.

With the advent of IBCTs, many of the mechanical steps present in RDE have been replaced with online access. However, from a practical point of view, the fundamental goals are the same (i.e. improve quality and reduce time requirements through the elimination of paper CRFs and double-key data entry). The main difference is the ability to have more sophisticated online edit and logic checks, there is an audit trail of changes, and data lock can

occur for data segments rather than by locking the entire database at one time. Sponsoring companies have 'real-time' data access, and query management is now a fully integrated online function. Data security is also a key business and validation issue. Fortunately, with the advent of encryption technology, data security can be properly managed.

The aim of this article is to provide a road map for the development of IBCTs and to share practical experiences, based on over 40 IBCTs in the US, Europe and the Middle East, which may help eliminate some of the frustrations when moving from paper to electronic data capture and data management systems.

1. Benefits of Internet-Based Clinical Trials

Clinical trials that use I-RDE/EDC could be invaluable for a company seeking to expedite the clinical development process. These benefits are discussed in sections 1.1–1.13.

1.1 Elimination of Double-Key Entry and Related Tasks

Currently, double-key data entry is one of the cornerstones supporting data quality. The way it works is as follows: (i) a paper CRF is filled out at the site; (ii) the monitor reviews the CRFs for accuracy and 'pulls' the sheets; (iii) the sheets are then sent to data management which logs them in and enters the data twice into two parallel databases; (iv) each 'double entry' is then compared, usually using a SAS-generated data-compare program – if the two entries correspond to each other, the data are accepted; if the two entries do not correspond, the correct entry is then determined and the incorrect entry is changed; if the data entry clerk cannot read a field, or the data are illogical or obviously incorrect, a query is sent back to the site to clarify or correct the data entry field; and (v) lastly, data listings are generated in SAS, and quality-control procedures are put in place to verify the data listings in comparison with the original paper CRF. At the time of the final quality control, all paper queries must be attached to each CRF to assure that all query resolutions are incorporated in the final database.

In web-based trials, these tasks are completely eliminated since the site enters the data, based on paper source documents, directly into the database through a web interface. Upon submission of the data, the system automatically checks for inconsistent, illogical, or missing data and sends back an error message. The site can then either change the data entry or explain why the data are 'correct'. All queries are managed electronically.

The critical difference is that with IBCTs, all clinical trial data are quality assured and entered at the 'front end' of the system instead of at the 'back end', as in the paper CRF paradigm. This saves a tremendous amount of time, as any resolution of queries takes place very soon after discovery and corrections are made in a

much shorter timeframe. As a result, there is quicker database lock and, in the case of time-sensitive interim analyses, an opportunity to quickly analyze reliable and quality-assured data.

1.2 Higher Quality Data Entry as a Result of Edit and Logic Checks at the Time of Data Entry

One of the main attributes of IBCTs is improved data quality. The main reasons for improved data quality are that (i) people who know the data the best, enter the data, and (ii) the online edit and logic checks pick up missing, out-of-range and potentially illogical data. There should also be minimal transcription and spelling errors. Out-of-range, missing, and illogical data are addressed in the comment field at the time of data submission to the hosting server. There is, therefore, an online explanation for data exceptions that can then either be accepted as 'OK as is' or queried by the study monitor. Missing and out-of-range data can actually be addressed prior to the monitoring visit. The clinical research associate (CRA) can now focus on source document verification and spend less or no time addressing missing and out-of-range data.

1.3 Online Treatment Allocation (Randomization)

The potential for online randomization is one of the most powerful and unique tools in IBCTs. Online randomization adds value in studies where there is a central randomization schema and/or stratification to treatment. Currently, when central randomization schemes are implemented, there is a central repository which is accessed via a toll-free telephone number to obtain the treatment code. If, on the other hand, allocation of patients can be performed online, then paper lists, envelopes, and dialing in to voice-activated toll-free numbers etc. could be eliminated. Also, when patient allocation is performed online, there is instant knowledge that a patient has been allocated and there is no need to call or be routinely informed as to the patient enrollment status. In addition, if errors in randomization occur, there could be instant notification to the appropriate staff at the sponsoring company. In the example shown in figure 1, after the YES button is marked under the question "Is the subject eligible for study allocation?" and the form is submitted, the treatment assignment is displayed just for the pharmacist. If for some reason the patient is not eligible for randomization, the NO button is marked and the reason must be given why the patient is not eligible.

1.4 Rapid Access to Patient Enrollment Data

In paper CRF-based trials, it is not unusual for the CRA to contact the clinical study site to report on the status of enrollment. The information is either given verbally or sent via fax. Once these

Is the subject eligible for study allocation? <input checked="" type="radio"/> Yes <input type="radio"/> No
Subject Number: 99A002 Treatment Group: Vehicle
If No, indicate reason for screening failure: <input type="radio"/> Withdrawal of Consent <input type="radio"/> Other Specify:
Race <input type="radio"/> Caucasian <input type="radio"/> Hispanic <input type="radio"/> Black <input type="radio"/> Asian <input type="radio"/> Other Specify:
Date of Birth __/__/____ dd/mon/yyyy Weight (Without shoes and overcoat)____ _ <input type="radio"/> lbs <input type="radio"/> Kg Gender: <input type="radio"/> Male <input type="radio"/> Female

Fig. 1. Example of a data entry screen with treatment assignment.

data are received by the CRA, the data are transferred to a file in either Excel or Word for presentation to the project team. With web-based trials, the data are always available in summary reports, which are accessible anytime, anywhere, and by anyone with proper authorization. For a sample report, see figure 2.

1.5 Rapid Access to Trial Data and Trial Progress

One of the most frustrating events in clinical research is determining the status of data entry into CRFs by the study site and which CRFs have been monitored. By using reports generated directly from the online database, the status of data entry and CRA review can be determined by the click of a button. For example, in figure 3, the sponsor has elected to perform a final review of each CRF page prior to 'locking' each individual form.

1.6 More Efficient Monitoring

Currently, site monitoring is one the most time-consuming and labor-intensive tasks in clinical trial management. It is not uncommon for site monitors to visit a study site and find out that the site is not fully prepared for the visit and that fewer CRFs have been filled out than expected. By using the reports discussed in section

1.5, both project managers and CRAs can assess when to visit the site based on the number of CRF pages that have been entered into the system but not reviewed in the field. Above all, one of the main practical advantages of IBCTs is that CRAs can now view the forms entered by the clinical study site prior to the monitoring visit. This can allow for a proactive approach to viewed problems as well as the ability to generate a query prior to source document review. This task can dramatically reduce the time involved in onsite monitoring and allow the CRA to focus on data quality issues and site management.

1.7 Decreased Number of Queries

Query management is one of the main tasks in data 'cleanup'. Queries can be generated by CRAs, medical monitors, and data management. With paper-based trials, query management is a labor-intensive process that is subject to errors. It is not uncommon for a paper query to be misplaced or misinterpreted. Going through a 'query book' or reconciling 'queries sent' versus 'queries resolved' can be a very frustrating process. With a built-in electronic query system, all query management is handled in a paperless manner and is managed via a computer screen rather than numerous paper forms in a ring binder. What used to take hours now takes minutes in a seamless operation.

The following is the series of steps of a sample electronic query system. The first step, as illustrated in figure 4, is a message from the sponsor that a query has been sent to the site. When the study monitor logs on, there is a message that indicates if there are any outstanding queries. There is no need to check a book, look up a log, or make a phone call. The second step is to address the query. When the monitor 'clicks' on "All cases", all patients with outstanding queries are displayed. The third step is to 'click' on the Subject number. When the subject number is clicked, the specific edit check, as seen in figure 5, is displayed. When the specific form is highlighted, the form is displayed with the associated comment from the site. In this case, the site acknowledges that the value is out-of-range but not clinically significant. As shown in figure 6, the CRA can then either accept the comment and then close the process by clicking on "OK as is", or generate an electronic query by clicking on the "Query: Click Here" button.

No.	Screening	Number allocation	Initials	Consent Form Date	Screening
1	99S003	99-003	JHC	01 Apr 2003	18 Mar 2003
2	99S005	99-005	LKS	20 Jun 2003	-----
3	99S011	99-011	WHY	02 May 2003	02 Jul 2003

Fig. 2. Subject enrollment log.

Site No.	Investigator	No. of subjects entered	No. of subjects allocated	No. of pages entered	No. of pages reviewed in-field	No. of pages reviewed in-house
01	Jones	18	17	282	66	22
02	Smith	22	16	166	88	15
Total:		40	33	448	154	37

Fig. 3. Enrollment and activity by site.

1.8 Elimination of Commercial Paper Case Report Forms (CRFs)

Paper CRFs are bulky and expensive to print and ship, take up storage space, and at times need to be changed during the course of a study. They also require three pages of no carbon-required paper for each page and have to be housed in relatively expensive binders. From a practical point of view, using electronic forms only involves a transfer of tasks from entering data onto a paper CRF to entering data onto a computer screen. Electronic forms can appear identical to paper forms, so nothing looks different from the perspective of the clinical study site that now has to enter the data. At the end of the study, electronic forms can be provided to each site in a human readable format such as a PDF (Adobe Acrobat). Therefore, when the US FDA arrives for a pre-approval inspection, all the site has to do is print out the CRFs of requested patients from a CD so that the FDA can compare the electronic CRFs to both source documents and data listings.

1.9 Instantaneous Alerts to Safety Issues

One of the most important assets of IBCTs is rapid access to safety data. Rather than have to go to each patient and extract summary data, a web-based system can display each adverse event. This allows medical monitors to easily and effectively review safety issues. A sample of a summary of adverse events from a specific study site is presented in figure 7.

Another feature of web-based systems is that they can allow for event alerts via e-mail, phone, fax, or other media at the time of occurrence. One example is patient dosage administration. When a drug is to be given per unit of body weight, the system can automatically compare the actual dose with the calculated dose and send notice of any errors. An example of such notification (e-mail) from an actual study is presented in figure 8.

Subject	Description	Date
QUERY	There are 5 outstanding edit checks that require your attention.	19 Jan 2003

Fig. 4. Message from the system that there is an edit check.

1.10 Electronic Signatures

Electronic signatures allow the principle investigator or designee to sign the CRF anywhere and at anytime as long as they have access to the Internet. There is no longer a need for a hard-copy signature. The electronic signature should not be invoked until the clinical summary page is 'locked'. There is no longer a need to give the principle investigator large numbers of binders of CRFs and wait for the signatures. In contrast, the principle investigator can review each completed patient record and sign off in a timely fashion from anywhere in the world. A record of 'locked', unsigned, and signed CRFs can be displayed to establish the status of the signature process.

1.11 Faster Time to Data Lock and Final Reports

When IBCTs are managed properly, forms can be 'locked' after review by in-field CRAs and/or in-house reviewers. If off-line edit checks generated by SAS® or through medical review find new issues requiring query resolution, new queries are generated to allow the study sites to enter the appropriate corrections. As a result of this ongoing process of data management, it is possible to complete all statistical analysis programming and data listing formats using 'blinded' data very early in the clinical trial process. Final analysis programs can then be run with unblinded data within 1–2 days of the last patients being monitored. Since the formats of all of the analytical tables are finalized prior to the end of the study, International Conference on Harmonization (ICH)-type study reports can also be finalized within 1–2 weeks after the final analyses.

1.12 Cost Savings

IBCTs should end up costing less than 'paper' trials because over time there should be more efficiency as a result of economies of scale. Even if in the short run it should so happen that IBCTs do not provide direct cost savings, the availability of 'real-time data'

Query no.	Form name	Field	Edit check details	Value	Entry date/time	View detail
001	Vital signs	Blood pressure (systolic)	Systolic blood pressure is out of range (85-140)	150	13 Jan 2003 13:16	Click here to go to edit check

Fig. 5. Example of an edit check.

for decision making and rapid access to final data analyses still makes the IBCT an extremely valuable tool in clinical research.

Table I addresses the tasks that change and the associated cost impact when an IBCT replaces a paper-based trial.

1.13 Cost Expenditures

There are several increased costs involved in setting up IBCTs. The most significant costs are incurred in the reorganization of the clinical development and data management departments to accommodate IBCTs, hiring a team of programmers to write source code, and setting up internal computer systems including the purchase of hardware and software and training. Alternatively, web applications can be subcontracted to companies with expertise in clinical trials. Following the initial set-up costs, there are only marginal costs for each additional clinical trial as well as fixed annual fees for system maintenance.

The basic technology necessary to execute web-based trials has existed for some time. As a result, there are no fundamental structural or technological barriers to the implementation of web-based clinical trials. Ideally, a web-based system should not require software installation or modem upgrades to high-speed Internet access. However, certain clinical study site-specific issues can arise, which when identified early in the process, can usually be easily addressed. These include outdated personal computers, old versions of Internet browsers, old computer monitors and network systems, and corporate Internet access policies.

To address these issues, an in-depth survey of the sponsor and clinical study site computer systems is carried out. In-house consultation must also be provided to each site to resolve any technical issues.

2. Structural/Organizational Issues

In our experience, the greatest challenge to the implementation of Internet-based trials lies within the organization of the sponsor-

ing company. Some clinical research personnel question efforts to move away from the use of 'tried-and-true' tools such as paper-based CRFs and point out that such tools have worked well for many years. In other words, "if it ain't broke, why fix it". There is little question that implementing a web-based clinical trial involves a new paradigm for clinical research. One way to make the transition is for senior management to identify a 'champion'. This individual should be motivated and committed to the program and overtly supported from the top. Another way is to provide in-depth training to all involved staff.

Prior to program commencement, a meeting agenda should be defined and all sponsor and system provider team members should meet and define the scope of the project. The team members should include (but not be limited to) those from the following departments: programming, data management, biostatistics, clinical research, quality assurance, information technology, and regulatory.

One very important caveat is that CRAs now assume some of the roles of the data manager. This conversion in thinking puts the onus of responsibility for data integrity together with the more common regulatory aspects of CRAs' function. Thus, the company must be aware that the CRA caseload must be adjusted as the CRA workload is redefined. The in-house data manager at the sponsoring company may also have a different role to play as a secondary, or in-house data, reviewer prior to overall database lock.

It is critical that during the initial project meeting, a contact person from both the clinical side and the system development side be assigned. These two people should be responsible for maintaining constant communication during system development and act as an interface between all other team members. At the initial project planning meeting, the following business rules and issues should also be discussed and/or defined:

- *System requirements:* since IBCTs require in-depth technology support, it is very important that the information technology

Field	Issue/answer	Value	OK as is/approve	Query
Blood pressure (systolic)	Systolic blood pressure is out of range (85-140).	150	Click here	Click here

Fig. 6. Example of option to respond to edit check.

No.	Patient number	AE name	Onset date	Stop date	Severity	Action	Relation	Outcome
1	01-12	Headache	23/Jun/2002	26/Jun/2002	Mild	None	Probably	Resolved
2	01-13	Nausea	21/Jul/2002	25/Jul/2002	Mild	None	Not Related	Resolved

Fig. 7. Summary of adverse events.

(IT) department be directly involved with all decision-making processes. The IT department must become familiar with Good Clinical Practice guidelines^[4] to ensure that the system is compliant with these guidelines as well as 21 Code of Federal Regulations (CFR) Part 11 and subsequent related guidelines.^[5-7] The IT department must also be aware of any technical limitations such as those of the clinical study sites, regional monitors, consultants, central laboratories, and in-house reviewers.

- *Defining deliverables, timelines, and expectations:* project planning is a key feature for the success of any project. However, with the paradigm shift in clinical trial management, planning is even more critical. Job functions may shift or even be eliminated, so there may be many concerned employees. For example, since there is no more data entry, there may be a need to shift these personnel to other tasks such as quality control during application development and final application release. The role of monitoring (e.g. identifying missing data) is reduced, but the role of auditing (e.g. whether a study has been performed correctly) increases. There may be a marked increase of in-house, online monitoring of clinical data.
- *Protocol and CRF design:* the process of protocol design is not different between a paper-based trial or an IBCT. However, CRF design is different, as there are conceptual changes to the

To: Pharma Company
Protocol 2001-01
Subject No 07-001
Initials GHT
Calculate the dose as follows: Body weight x 1.5
Dose calculated by system: 105mg
Dose entered by pharmacist: 125mg
Difference: 19%
Body Weight: 70 kg
Comment: Since the dose difference is greater than 7.5%, the Medical Monitor will contact the Pharmacist and validate the dose.

Fig. 8. Example of an automated e-mail alert to a dosing error.

functionality of the entire EDC system. For example, there is no longer a need for multiple pages for adverse events and concomitant medications, as the form appears only when there is a positive answer for the presence of a new adverse event or medication. If the answer is negative, then the form does not appear. A CRF must be designed to allow the computer systems to perform efficiently. The edit and logic checks should not be hampered by unnecessary requirements. Since upfront programming is involved prior to study implementation, and some of the logic can be complex, changes to protocols prior to study implementation should be kept to a minimum after the commencement of programming.

- *Project flow including roles, responsibilities, and needs:* since execution of the clinical program is an integrated team process, it is critical to decide upfront what the features of the system are, how the system will be implemented, and what the defined tasks for each study participant are. For example, what is the patient numbering convention? Who is authorized to enter data? Who is authorized to modify data? Who is authorized to manage the query process and approve deviations?
- *The monitoring process:* while the end product of monitoring (i.e. source document verification) is no different with the introduction of IBCTs, the process is different. The main difference is that the monitors are much more knowledgeable about the status of the trial even before the monitoring visit. Each form can be reviewed prior to the monitoring visit, and if the data seem acceptable, the form can be marked as reviewed. If the site changes the form prior to the monitoring visit, the form can be marked as unreviewed, which informs the monitor that the form has been modified. The monitor can also have the authorization to lock the form to prevent personnel at the site, prior to authorization, from changing data after the monitoring visit. All of these tasks are reversible until the final data lock at the end of the trial.
- *Database specifications:* since the database must be created prior to data entry at the study sites, the database structure must be finalized before the study starts.
- *Standard operating procedures:* IBCTs require the creation of new standard operating procedures. The key standard operating procedures must address the requirements of 21 CFR Part 11, such as the rules for electronic signatures, the need for time and

Table I. Task comparisons of paper-and Internet-based clinical trials

Task	Paper-based trial	Internet-based clinical trial	Cost for EDC
Case report forms			
Original	Yes	Yes	Same
Printing	Yes	No	None
Shipping	Yes	No	None
Changes	Requires printing and shipping	Online and immediate	Less
Storage	Physical warehouse	CD or other media	None
Storage cost	Yes	No	None
Data management			
Data entry screens	Yes	Yes	More
Data management set-up	Yes	Yes	More
Data entry	Double-key by sponsor	Entered by site once	Less
Missing/illogical data	Problem resolution after site visit	Problem resolution prior to site visit	Less
Validation checks	SAS® (offline) program edit and logic checks	Most at the time of data entry	Less
Query management	Paper forms with delays	Instant electronic record	Less
Data audit	Paper forms	Electronic audit trail of changes	Less
Monitoring			
Location	All done in field	Combination field and office	Same
Problem resolution	Problems identified at site	Many problems identified in advance	Less
Project management	Information via fax and phone calls	Instant electronic report	Less

EDC = electronic data capture; **SAS** = statistical analysis system.

date stamps within the audit trail of changes, security, data integrity, validation, and site registration and authorization procedures.

- *Edit and logic check specifications:* online edit and logic checks provide a major contribution to data quality. One main concern when designing these checks is not to make them too restrictive. When an EDC system is designed to replace the paper function, the quality of the data must not be lower than current standards.

3. Areas of Cost Savings in Internet-Based Trials

The cost-saving potential offered by IBCTs is substantial, and can increase significantly as the size of a trial increases. In this section, estimated cost savings for a 40-center study with 1000 patients and a 100-page CRF are presented. A summary of savings is found in table II.

3.1 Printing of the CRF

CRF printing costs can run as high as \$US100/book (2003 values). For 1000 patients, this represents a cost saving of up to

\$US100 000 (2003 values) with an IBCT, not including the staffing resources necessary to ship the CRFs and the direct shipping costs themselves.

3.2 Double-Key Data Entry

This cost can be as high as \$US6/page. For a 100-page case book and 1000 patients, this represents a cost saving of up to \$US600 000.

Table II. Summary of the estimated direct cost savings of a multicenter study

Tasks	Cost savings (\$US; 2003 values)
Printing of CRFs (\$US100/book)	100 000
Double-key data entry (\$US3/page by 2)	600 000
Data QC (\$US6/page)	300 000
Query management (\$US50/query)	362 500
One less trip (\$US3000/trip)	120 000
Total estimated cost savings	1 482 500

CRFs = case report forms; **QC** = quality control.

3.3 Query Management

In a case study comparing a paper query management system with an electronic online system using edit and logic checks, there was an approximate 65% reduction in queries.^[8] For a paper CRF system, there was an average of one query per six CRF pages, not including queries generated at the time of data entry. In the IBCT, there was one query in every eight pages. For the hypothetical study being discussed here, there would be a reduction from approximately 16 000 CRA-generated paper queries to approximately 8750. Using an estimated in-house cost of query management of \$US50/query, there would be a savings of approximately \$US362 500.

3.4 Monitoring

Since many monitoring problems can be identified in advance, at least one monitoring trip can be eliminated and the monitoring time spent at the site during the remaining visits can be minimized. Even if just one trip and an additional 1 day of monitoring is saved for each of the 40 study sites in our hypothetical case, the savings for 1 day of travel, 1 day of monitoring, and travel costs could run up to \$US3000/site. The total savings in this case would be \$US120 000 ($\$US3000 \times 40$).

4. Practical Recommendations

No matter how sophisticated or unsophisticated one's IBCT system is, if it is not user-friendly there will be resistance to its use and it will eventually fail. As a result, it is critical to incorporate ideas and suggestions from experienced designers and users of EDC systems and not to take the attitude that if it 'was not invented here' (NIH) it has no value. Also, it may be advisable to evaluate several approaches before committing to a system. However, do not procrastinate since IBCTs are here to stay.

4.1 Simplify Data Entry for Study Site Personnel

The ultimate customers of IBCTs are the clinical study sites. It should not be forgotten that the main goal of an IBCT is to obtain high-quality data in a rapid fashion. If you ensure that your system is easy to learn, you will reduce training costs and minimize errors.

4.2 Minimize Between-Form and 'Hard' Edit (Validation/Logic) Checks

There can be a tendency to make EDC systems completely logical so that it is virtually impossible to enter inconsistent or illogical information. This can be done both within a form and between forms. Between-form edit checks can sometimes create problems, especially when there is an attempt to enter data from

later visits before data from a prior visit are entered. Also, most edit checks should be 'soft' so that if a field is out of range or illogical, an explanation can be provided in the comment field. In contrast, hard edit checks, which prohibit a form from being submitted, must be minimized since it is not uncommon to have unanticipated exceptions.

4.3 Hybrid Systems

Conceptually, there are three types of data entry systems. One type is server based, which does not require software installation on the client's computer. Server-based systems offer the advantage of complete centralized management of both data and applications. The second type installs the entire system on the client computer and allows for off-line batching of data to be submitted to a server. This is similar to classic RDE. The third type, a hybrid system, allows for both immediate transmission of data to a server, and off-line collection of data, with batch delivery at completion of the work day.

Hybrid systems offer many advantages over both RDE and server-based systems, since processing in hybrid systems is distributed to both the client and server. Hybrid systems also offer the advantage of distributed computing between the server and client, which can maximize resource utilization. However, with classic RDE and hybrid systems, because the data reside on the client's computer for a period of time, there are potential issues of data integrity that must be addressed in the validation process. In addition, hybrid systems have higher maintenance costs than server-based systems, since software must be installed on each computer. Hardware may need to be purchased or upgraded to allow for compatibility with the new software. Also, when changes to CRFs are required during a study, the amended software must be installed.

4.4 Choosing a Vendor/Partner

Choosing a vendor in the EDC world is the equivalent of choosing a partner. While technical competency is a given, consideration should be given to flexibility of the system, intrinsic features of the system, financial stability and experience of the company, limitations of the product, costs, and other business concerns. However, one of the major factors to consider is: "How well can I work with the vendor and how responsive will they be to my needs and perhaps even to my wishes?"

5. Metrics (Measurements of System Performance)

In a previous publication, Mitchel et al.^[8] reported that for a traditional paper CRF study in the area of infertility, with 192 patients and 11 130 pages entered by data entry clerks, there were

a total of 0.264 queries per CRF page. This included queries generated by both monitors and data entry clerks at the time of double-key data entry. In contrast, for a comparable size IBCT study with 191 patients and 7908 CRF pages entered by the study site, there were 0.118 queries per page.

A second study evaluated both the total number of generated queries and those generated as a result of online computer-generated edit checks. The study was a 12-center clinical trial with 193 patients with periodontal disease. Results showed that there was a total of 1124 queries generated by the CRAs out of 8972 forms entered (0.125 queries/page). Of these queries, 137 were generated as the result of online edit checks, while 987 were generated by the CRA for action or clarification. Of the 1124 queries, 65% were designated "OK as is" which meant that the response to the query required no changes to the database. Only 35% of the queries required action by the clinical study site. Out of the 8972 entered pages, there were 597 edit checks generated (0.067 edit checks/page). Of these edit checks, only 137 (27.3%) required a query to clarify the edit check. The remaining 460 (72.7%) required no action by the study site and were designated "OK as is".

6. Confidentiality

There is now major concern in both the EU and US about maintaining the confidentiality of patient data, especially when using the Internet. In general, clinical trial data captured by IBCTs do not have patient identifiers other than initials, a study specific number, sex, and date of birth. All transactions via the Internet should be encrypted and only the investigator should know the personal information of each patient. Unless required by regulations and only after providing informed consent can certain personal data be revealed to other involved organizations (such as sponsors, Contract Research Organizations [CROs] and regulators).

7. Discussion

One of the main advantages of IBCTs is that the people who know the data the best (i.e. those at the clinical study site) enter the data directly into the database. There are no judgments of intent, no illegible fields, and no symbols that require interpretation. In addition, all missing and out-of-range data are flagged and require explanations at the time of data entry. Either before or during monitoring, data discrepancies can be confirmed. In terms of data quality, Mitchel et al.^[9] demonstrated that data capture in an IBCT had a very low error rate, and any errors observed were related to human activities and not related to underlying technology.

In 1997, the FDA issued a regulation contained within 21 CFR Part 11 which addresses the use of electronic signatures and

electronic records.^[5] In 1999, the FDA issued a guidance to address issues pertaining to computerized systems in clinical trials used to create, modify, maintain, archive, retrieve, or transmit clinical data intended for submission to the FDA.^[6] Although the primary focus of the guidance was related to computerized systems used at clinical sites to collect data, the principles in the guidance are also appropriate for computerized systems used at CROs, data management centers, and by sponsors. The goal of the guidance was to assure individuals using the data from computerized systems that they should have confidence that there is data integrity and that data entered electronically were no less reliable than data collected in paper form. The FDA has recently issued two guidances regarding electronic records and signatures^[7] and general principles of software validation.^[10] In order to comply with 21 CFR Part 11, all changes to the database are to be automatically tracked including an electronic stamp of who changed the data, the date and time of the change, and the reason for the change, if required. If electronic signatures are used, the standard operating procedure for sign off must conform to the requirements of 21 CFR Part 11.

8. Conclusion

Within 2 years, sponsored clinical research, by necessity, will use some form of Internet-based system to assist in the conduct of clinical trials. This will occur as: (i) the prices for Internet-based systems fall with more competition; (ii) there is increasing confidence in the use of electronic data; and (iii) economies of scale develop as studies with similar designs, architectures, and business rules are implemented. The benefits of IBCTs are in the area of randomized clinical trials, as well as in the areas of postmarketing clinical trials, patient registry studies, and project and safety management.

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While Target Health Inc. has its own proprietary electronic data capture system, there are no direct cross-references to the Target e*CRF™. The only material taken from our system are screen shot examples and are not unique to our system.

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