



I N T E R N A T I O N A L

Managing Research Information Worldwide.

**DOES YOUR EDC PRODUCT COMPLETE ITS
CASE REPORT FORM IN PENCIL?**

Dr. Jeffrey A. Green
President & CEO
DATATRAK International, Inc.
Cleveland, Ohio and Bonn, Germany
(Nasdaq: DATA)

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I. Introduction

Worldwide, the clinical research environment remains largely a paper-driven process. Estimates vary, but it is presumed that currently 90-95%^{1,2} of all clinical trials utilize paper as the recording medium. This percentage is predicted to steadily decline over the next few years secondary to a greater rate of implementation of technology in the data collection and review process¹. Some sources predict an adoption rate of electronic data capture (EDC) in clinical trials of 14% by 2003 and 24% by 2004 across the global market¹. Thus, careful comparisons of paper and EDC workflows, with specific scrutiny being applied to the vast number of available technology products and platforms, will be necessary in order to properly guide this transition with the least regulatory risk to the sponsor.

This author knows the paper process well having been an investigator on approximately 100 clinical trials for many sponsors and Contract Research Organizations (CROs) where appropriate behavior was conditioned and governed by both SOPs and the predicate rules of Good Clinical Practices (GCPs). Subliminal messages on the quality of a clinical research site and its staff can certainly be measured in the paper model by the degree of “yellow sticky toxicity” present at the end of a monitoring day.

This specific White Paper will address only one small, but critically important aspect of the case report form (CRF) process in clinical trials that deals with how these data sheets are completed and edited. As expected, such activities are highly regulated by sponsors, the United States Food and Drug Administration, and other International Agencies. Examination of this “CRF completion/editing process” will be done in the context of both paper and technologic models of workflow.

II. Completing/Editing a Case Report Form in the Traditional Paper Process

No specific reference can be found in the most recent printing of *The Code of Federal Regulations on Good Clinical Practices* (revised on April 1, 1999) that instructs

investigative personnel to formally enter data into a paper CRF in pen only. However, according to interviews with several compliance officers, experienced Clinical Research Associates (CRAs), and investigators with decades of experience, most, if not all pharmaceutical companies and CROs specify such a SOP of completing the paper CRF through the use of a pen. Therefore, it is a logical presumption that sponsors have actually adopted a more stringent and specific internal regulation related to this single aspect of clinical trial behavior – more than likely, under the belief that fraudulently entering data in an undetected manner with pen is harder to accomplish than with pencil, since with graphite, answers can be erased and reentered more easily. Though not officially in violation of GCP Regulations, CRF entries in pencil would make credible monitoring of a clinical trial much more challenging and risky to defend as accurate. Of course, virtually every company SOP in this industry also prohibits the use of “White Out”, since this functionally transforms the pen-based process to be almost in parallel with the pencil-based entries, since interim answers are disguised and probably rendered unreadable.

Anyone familiar with the clinical trial process knows that a virtually universal activity surrounding the alteration of clinical trial data on a paper CRF involves drawing a single line through the changed field, accompanied by the date and initials of the individual making the modification. Such a process is also commonly used in editing and reviewing legal agreements of many kinds, indicating that the activity associated with content changes in formal documents belong to more than just the relatively limited environment of clinical trial work.

GCP guidelines direct these actions, though as Regulations go, their official requirements are more general. They read as follows from Section 5.18.4 under “Monitor Responsibilities” on page 36(n) of the pocket version:

“[The monitor should] inform the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by

a member of this investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented."

Notice the specific wording of the regulation does not mandate entries by pen, but that "**any CRF entry**"... should be tracked by some appropriately implemented process. In the English language, "any" means **ALL**, not some select number or just the "final answer".

Furthermore, in Section 8 of the GCP Regulations entitled, "***Essential Documents for the Conduct of a Clinical Trial***", the Table on page 59 of the pocket version specifies under 8.3.15 pertaining to the "Documentation of CRF corrections" that the purpose of this document is "To document **all** changes/additions or corrections made to CRF after initial data were recorded".

Importantly, in addition to the concept of tracking as suggested from the foundational information in the previous paragraphs, it is also clear that *initial* data entries with paper models of CRF completion do not carry the identical rigors as *changes* to the data. Initial entries require no audit trail in the current GCP Regulations. Changes to data entries do require an audit trail. Possible problems with the paper model of data entry examining this exact scenario will be highlighted in the small case study later in this White Paper.

II. Electronic Data Capture and Audit Trails

EDC is a growing paradigm that has just begun to emerge globally in an increasing proportion of clinical trials. Data on the ability of appropriately selected and administered products and services indicates that EDC positively impacts each one of the "trinity of factors", namely, Quality, Time and Cost³. The overall value proposition of EDC to the pharmaceutical industry is compelling and worth in the \$50,000,000 - \$100,000,000 range in either added value and/or reduced cost, compared to paper^{1,2}.

However, with specific reference to the modification of data entries or audit trails referenced in the GCPs, when considering EDC products and platforms, sponsors should

be aware of important technical differences as to how this information is eventually tracked in a study database following entry into the electronic case report form (eCRF). The GCP section dealing with this activity is listed formally under Section 5.5, entitled “Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee”, which appears under the broader category, Section 5 of “Sponsor” (responsibilities). Section 5.5.3 (on page 27 in the pocket version), (in part) specifically states,

“When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).***
- (b) Maintain SOP’s for using these systems.***
- (c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).”***

The critically important portion of this Section clearly indicates that the GCPs require that the use of electronic data collection systems conform to the sponsor’s established requirements... - meaning in most clinical trials – filling out your CRF in pen, not pencil; with all of the intended aspects of the pen model enforced in the optional use of an electronic system. Federal regulations have always been visionary in such adoptions of technologic advancements, they just place the burden on the industry at large to make sure we all advance with the implementation of technology and not lessen our vigilance hastily for the sake of “moving forward”. Implementation of EDC should provide for no less scrutiny than paper methods in any aspect of clinical trial data collection and review.

In the front of the Revised GCP Guidelines dated April 1, 1999, the Glossary Section on page 3 defines an Audit Trail as the following:

“Documentation that allows reconstruction of the course of events”

Though there is latitude in the interpretation, it is presumed that such a reconstruction of events should be total, rather than partial - though once again, the specific mechanism(s) as to how this requirement is satisfied is left up to the individual sponsor. Consistent with the theme of this White Paper in analogizing EDC with paper, this is handled by almost all sponsors through completion of the CRF in pen with single lines drawn through every alteration (taking the liberty that “every” is synonymous with “any” and “all”).

Given the background already presented, it is imperative that sponsors recognize that all EDC products/platforms are not identical, and that appropriate research be done prior to the ultimate selection of an electronic solution so that as much consistency as possible is present between the proven paper models of clinical research and technology applications. Each sponsor’s Regulatory Departments must be comfortable with the audit trail process deployed to ascertain that the excitement of achieving the significant value proposition of EDC is properly counterbalanced by a comfort that the selected technology is not sacrificing vigilance in favor of being “trendy”.

Table I briefly summarizes three generic mediums and/or platforms for data collection at a research site. The first column and first row includes the time-tested medium of paper. The second and third rows include three different mechanisms currently used in the market to capture audit trails with EDC – namely, Hypertext Markup Language (HTML) an 18-year old computer language initially created for the sharing of documents, HTML combined with the downloading of JAVA script onto client machines, and server-based implementations utilizing Independent Computing Architecture (ICA) applications from Citrix. The Specific products or companies using such EDC implementations are not mentioned. This due diligence is left up to the sponsors in order to make sure that their choices satisfy as much as possible the intents of the predicate rules governing GCP.

Table I. Comparison of Paper, HTML/JAVA Script, and Products Implementing Data Item Tracking on Audit Trail Parameters

<u>Collection Medium</u>	<u>Method of Audit Tracking</u>	<u>Time Audit Trail is Documented</u>	<u>Audit Tracking Voluntary or Automatic?</u>	<u>Is Every Field Entry Traceable? (i.e., identity, exact time, etc.)</u>
Paper	Original entry inexactly assessed by comparison to SDV; Changes by lined out data item, date, and initials	Usually weeks to months after data entry; physical monitoring visit required; therefore, Source Data is necessary for an estimation to be done with the initial data entry	Voluntary, but enforced by GCP Regulations and SOPs of the monitor; Compliance is left up to the user to actually enforce; verification of initials requires handwriting “assessment”	No
HTML/JAVA Script	Following a page submission	Upon page submission	Automatic	No*
Limited Number of Products	Data Item Level **	Upon leaving an individual field	Automatic	Yes

*In most current deployments this answer is no. To make this answer yes, validation challenges would be significant. ** A data item is defined as an individual, complete answer for a field. For example, a birth date is a data item and a weight is a data item.

There are several important points that can be made from a careful examination of Table I. The first point, which is not obvious unless the paper model is compared against the capabilities of EDC, is that initial data entries into a CRF have no confirmatory audit trail (nor are they required to have one according to GCPs). It has widely been assumed that if the source document matches the original entry into a field, that a level of comfort is reached during a monitoring visit that the time sequence and the identity of the individual entering that data are obvious. However, neither the responsible identity, nor the timing of the original data entry can be confirmed in the traditional paper model. In order to better illustrate this point, please see the actual case study briefly summarized on the following page.

Case Description

Fraud was suspected at a clinical research site when entries into an EDC system were noted to have occurred 31 days apart *within* the same visit date in a particular study. The system was appropriately being utilized in this study as the Source, according to regulations as specified in 21, CFR Part 11. Upon remote review of the data, the sponsor questioned the ability of the research personnel to remember events that occurred a month before the actual data entry into the EDC system. Spawning further investigation, the sponsor ascertained that four (4) complete visits were entered into the system within a six (6) minute period of time.

In this case study, the initial concern over fraud would have never arisen in the paper model of audit trail tracking, since the initial entries are not required to be time, date, or identity stamped. The presumption in this case was that data was being “manufactured” and could have been appropriately and neatly written into the paper CRF without any credible, confirmatory, examination possible by the monitor visiting the research site. Even entries with different color pens could have been easily explained away as part of a normal monitoring visit with only minimal suspicion possible regarding the temporal difference between actual data collected and final entry into the CRF. The specter of concern could easily and remotely be investigated because EDC was being used in this study that automatically tracked the audit trail upon entry of even the initial information. A physical monitoring visit was not necessary in this case in order to evaluate aspects of data entry, and such an “assessment” would have been impossible in the paper model. In the paper model at worst, this scenario would have never been detected and at best would have been suspected weeks to months later after possibly more data had been “manufactured”.

As also can be seen from Table I, not all EDC systems or implementations are capable of tracking **“any and all”** CRF entries, as specified in the predicate GCP Guidelines. Few systems track data entries on a field basis, and most HTML/JAVA-based implementations track audit trails on a page level basis (which includes multiple data items). This means that **“any and all”** entries into an eCRF are not necessarily tracked, but are committed to the database only upon submission of the page. This can be interpreted as filling out one’s CRF in pencil, with intermittent answers never made

available for review or examination by the sponsor. In this respect, and in the use of such platforms, the paper model is actually more diligent than technology.

These audit trail-tracking differences can be most dangerous when one considers some technologies that are capable of downloading JAVA Applets onto the client machines of the investigative staff in order to apply the efficiency of edit checks or validation routines appropriate for the protocol **BEFORE** the final submission of the page that commits the accompanying audit trail to the database. Allowing an investigative staff the ability to “manipulate” data entries based upon nonviolation of either inclusion or exclusion criteria of a protocol while being absolutely unable to track **“any and all”** entries appears dramatically inconsistent with the predicate rules enveloped in GCP and properly enforced by sponsors worldwide. It is conceivable and technically possible that investigative staff with impunity can “fit” data into a study while actually being assisted by the accompanying guidance of the range checks downloaded by the JAVA applets. In the paper corollary, this would be akin to making multiple entries into a field in pencil, assessing whether they are in range or not, and then erasing unwanted interim answers (or using “White Out” in the pen-based model) while submitting the “final answer” in such a way that the monitor could never detect how many actual entries had truly been made.

Though some technical platforms have removed the edit checks and validation routines from the time of initial data entry, and have relocated such activity to the back-end of the data management process in order to enhance sluggish performance and augment user satisfaction (because of faster page turns), this action destroys a major economic and process advancement for the industry. It has been well demonstrated that by properly moving the edit checks and validation routines ahead to the time of investigative staff entry of data, the quality and speed of data movement through a clinical trial can be positively impacted, with Query rates being diminished by >80% ³.

III. Perspective/Summary

The pharmaceutical industry has tried for decades to enhance the process by which data can be collected and reviewed globally. With the rapid growth of the Internet, there reside great possibilities of advancing our paradigms forward for the benefit of society as well as the industry at large. The “trinity” of metrics (Quality, Time and Cost) have been demonstrated to be improved with the implementation of EDC and the ability to “live” with one’s data, anytime, anywhere, gives the clinical trials industry additional advantages that have not even been fully appreciated or evaluated and, importantly, such capabilities are impossible with paper models of data collection.

One clear advantage of data collection and review with EDC certainly improves the paper paradigm through the tracking of initial data entries (as exemplified by the case study) and offers a security level for the ability to enter data into a CRF beyond what is possible with three-ringed binders (user names and passwords are not necessary to enter data into a three-ringed binder).

However, the industry must be careful to appropriately use technology to truly advance beyond the paper model in other areas as well. We should be careful not to get “caught up” in the technical enthusiasm and make excuses to bypass workflow that has been successfully used for decades simply so that we can “run our trials on the Web” or benefit economically to the detriment of safety and the ability to detect fraud.

As can be seen in Table I, there are critical differences among EDC products and platforms in the ability to track audit trails. Importantly, each and every one of these products and platforms may indeed be compliant with 21, CFR, Part 11 – meaning that the audit trail is logged when the appropriate data is committed to the database in the normal functioning of the “system” – whether that be on a data item or on a page basis.

However, just as with the pen vs. pencil example in the GCPs, the Regulations do not specifically say what type of writing instrument is to be used in the collection of paper

data – nor do they state exactly how audit trails are to mechanistically function. The global pharmaceutical industry has taken this latitude to “go beyond” what is “written in black and white” to establish a standard themselves that a pen, and not a pencil, is to be used to enter data into a paper CRF. Does it not make logical sense that the “improved” technology paradigm would ideally implement the identical “higher standard”?

Arguably, from more of a clinical perspective than a regulatory one, clinicians will want to diminish as much as possible even the remote possibility that data can be “massaged” at the time of entry before they are ever committed to an audit trail, though the current Regulations do not declare that the ability to enter data multiple times into a field is a violation before it is committed to the final database. Most clinicians should want to know exactly who and when a data field has been “touched” in an eCRF. After all, most global Quality Assurance Officers would certainly question erasing data entries in pencil, and few would declare as advancement the use of technology that allows this to occur.

Sponsors need to be cognizant of the fact that Regulations advance with proper education and supported rationale, and it appears clear to many that tracking audit trails on a data item basis more closely aligns with the current practice of sponsors as well as the spirit of the predicate GCP rules which were written with paper, and not EDC, in mind. In a conservative industry such as this, compliance officers must be brought into the decision process of EDC data collection to make sure that the process of audit trail tracking with EDC is at least as vigilant as that with the proven paper model.

As the pharmaceutical industry has “raised the bar of practice” beyond what is actually written in the GCPs by enforcing collectively the use of pen entries instead of pencil, sponsors need to make sure that they can “sail well above the requirements” as they move into the EDC model of the future.

REFERENCES

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