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Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane – Room 1061
Rockville, MD 20852

Docket ID: FDA-2010-D-0643

RE: Draft Guidance for Industry: “Electronic Source Documentation in Clinical Investigations”

To Whom It May Concern:

Clinical Ink is pleased that the FDA has taken this initial step to clarify the acceptable use of electronic source documentation in clinical investigations. Dr. Thomas W. Littlejohn, III¹, an experienced investigator who served as a PI and oversaw thousands of clinical studies, co-founded Clinical Ink four years ago with the goal of developing an application specifically designed to eliminate paper source documents at research sites. In fact, Dr. Littlejohn played a small role in some of the earliest thinking about the topic of eSource in a discussion with former commissioner Von Eschenbach several years ago.

In addition to Dr. Littlejohn, Mr. Edward S. Seguire and Mr. Douglas E. Pierce also participated in the compilation of these comments. Mr. Seguire is an experienced clinical technology executive having worked at Medidata, one of the largest EDC providers; at Fast Track Systems (as the CEO), which developed the first structured protocol authoring application; and at Eli Lilly’s technology venture capital group. Mr. Seguire has extensive experience with CDISC standards having served nearly five years on various CDISC board committees and as chair-elect of the CDISC Industry Advisory Board. Mr. Pierce founded Piermed, Inc., a medical documentation business and has been actively working with source documents and eSource applications over the past four years.

Our collective experience informs our perspective in multiple dimensions: the workflow impact at a site, the implementation effects of the technology and data recommendations, and the business operations implications for sponsors/CROs. Importantly, the Agency must recognize that this guidance will provide a roadmap many years into the future and must guard against using terminology and suggesting frameworks that may, in fact, hinder progress by anchoring too firmly to existing constructs.

With that backdrop, we offer the following comments and suggestions:

1. Terminology: Our primary concern with the guidance is that it dramatically expands the accepted definition and practical use of the term ‘case report form’. The term CRF, whether it is paper or electronic, has a very defined meaning both in practice and in existing guidance^{2,3}. Generally speaking,

¹ Tragically, Dr. Tommy Littlejohn was killed in a small plane crash on Wednesday March 30, 2011. He had been working on these comments at the time and looked forward to helping shape the final guidance. Other members of the Clinical Ink management team have completed these comments on his behalf.

² ICH E6 1.11 - A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject

a CRF has traditionally been limited to conveying only that data required by the sponsor for analysis; the analysis dataset represents only a subset of all the information and documentation about a trial. In contrast, the source documentation at a site is much more expansive and covers the entirety of documentation necessary for the investigator to establish a robust case history (21 CFR 11 parts 312.62 and 812.140), as well as to provide evidence of compliance with GCPs and protocol-specific procedures. The draft guidance proposes to alter/adapt the term ‘case report form’ (CRF) as the overarching organizational construct for electronic source information. The term is first used in this way in lines 96-99 and that interpretation is compounded by the inclusion of Figure 1 where the eCRF is depicted as the central collection mechanism for all data.

We note that other publicly available comments also point to the confusion that results from expanding the definition of a case report form:

- Medimmune comment #1 recommends that the title be changed to acknowledge the impact on the setup and population of the eCRF.
- Gen-Probe’s comments on the title of the document and the figure indicate the confusion created by imbuing the term CRF with a much more expansive meaning.
- Triangle PEERS page 8 makes the same argument that the term CRF “has acquired a precise meaning within industry. . . as a result, industry’s common frame of reference for what constitutes an eCRF is not consistent with its broader usage in the draft Guidance.”

Rather than expanding the definition of a case report form, Clinical Ink strongly supports the use of the term ‘electronic source record’ (ESR) and believes that the term should be used liberally throughout the guidance. We note that the Glossary, line 475, defines the term ‘electronic record’ and that the term ‘electronic medical record’ (EMR) has become commonplace when referring to subject medical records. We suggest that the term ‘electronic source record’ is a more encompassing description that includes documents and data (lines 42 & 43) as well as other types of information⁴ (see also lines 488-495) as contemplated in the definition of electronic record. An ‘electronic source record’ can also be considered distinct from an electronic medical record because the definition of ‘source’ for clinical trials has a very specific understanding (see ICH E6 sections 1.51 and 1.52 – note also the use of the word ‘record’ in the definition of source data and the reference in section 1.43 to ‘original medical records’ which refers to source documents).

We believe there is ample precedent and context (both regulatory and in common usage) to introduce the term ‘electronic source record’ as being a compilation of various types of source data and documents in an electronic format. We also believe that this term will have greater longevity – the concept of a case report form is fundamentally rooted in the arcane practice of recording information on paper, transferring a portion of that information to a separate document, and recording that subset of information into the clinical database. Over the relevant life of this guidance that practice will definitively become outdated – particularly if the concept of eSource becomes well accepted. We

³ A text search of ICH E6 reveals 25 separate instances referring to a “CRF” and the specific procedures, data, or information associated with the CRF. Another three instances refer to the word ‘case report form’.

⁴ ICH E6 8.3.13 defines the purpose of source documents to be, “To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.”; 21 CFR 11 Part 312.62(b) “Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.”

respectfully request that the agency adopt the term “electronic source record” rather than complicate the established definition of “case report form”.

2. Introduction: We commend the agency for explicitly articulating the specific aims the guidance is intended to promote. Clearly communicating the intent provides a critical lens through which the specific wording throughout the document should be interpreted. In particular, we recommend that the agency retains lines 20-26 in the final guidance.

3. Background: This section provides a very helpful discussion of paper versus electronic documentation. It is our recommendation that the agency incorporate wording similar to that used by the European Medicines Agency in comparing/contrasting paper and electronic source and the processes that support each approach:

“Source data and transcribed data have traditionally been recorded in paper documents. Many requirements and expectations have been developed in this context. *The principles underlying these expectations and requirements are largely applicable to electronic media but their practical application is different.*”^{5, 6} (*emphasis added*)

Furthermore, it is recommended that the agency make reference to ICH E6 2.10 which states “All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.” This standard for quality documentation should be reiterated as being equally valid in an electronic source environment, albeit in a different format than paper.

A statement such as this serves to put the focus on higher level principles rather than specific, narrowly interpreted standards the application of which would be slightly different in an electronic environment versus paper. Clinical Ink believes that an acknowledgement that the same result can be achieved through different processes is essential to increasing the usefulness of the guidance over a period of time during which the technology will undoubtedly be changing very rapidly. This suggestion is similar to the type of language the agency has used recently in other final guidance.⁷

It is our recommendation that similar language be inserted as part of the paragraph ending on line 68.

We agree that the *data element* is the basic unit of information but, with respect to our concerns regarding the use of the term CRF, it is our recommendation line 71 be truncated to eliminate the wording “in the eCRF”.

4. Electronic Source Documents and Source Data: As previously mentioned, we believe that much of the potential for confusion stems from the dramatically expanded scope and role of an electronic case report form. Beginning in line 96 and throughout the discussion of Figure 1 there are multiple

⁵ European Medicines Agency, “Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials”, June 9, 2010; page 5.

⁶ ICH E6 4.9.3 specifically states the process for documenting a change or correction to a paper CRF. Obviously, the specific steps for making changes in an electronic source environment will be different.

⁷ Final Guidance “Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects”, October 2009, page 2, “Although specific investigator responsibilities in drug and biologics clinical trials are not identical to the investigator responsibilities in medical device clinical trials, the general responsibilities are essentially the same. This guidance discusses the general investigator responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.”

references to the centrality of an eCRF. Rather than have the eCRF serve as the “vehicle to assemble all the data. . . in a manner that satisfies the study protocol and enables the data to be systematically reviewed and analyzed”, it is our recommendation that lines 96-99 be removed entirely.

The physical exam is a good example of the inadequacy of the case report form structure. Most case report forms simply ask if the medical exam was normal or abnormal (see Appendix A for actual examples of a physical exam CRF versus a source document). Source documents, however, must also provide objective evidence that the investigator, who makes a signed commitment⁸ to safeguard the subject’s welfare and safety, has comprehensively evaluated and documented the condition of the subject. As a consequence, site source documentation of a physical exam will generally include multiple body systems that the investigator must assess, determine if the condition is normal or abnormal, and then evaluate whether the condition is clinically significant or not along with any observational notes. Because CRF design is always driven by the data needs of sponsors, not the broader compliance needs of investigators, the CRF typically has only those fields the sponsor wants to analyze and is inadequate from the standpoint of providing a comprehensive means to document the overall condition of the subject.

We recommend that Figure 1 be replaced with a figure similar to that shown below:

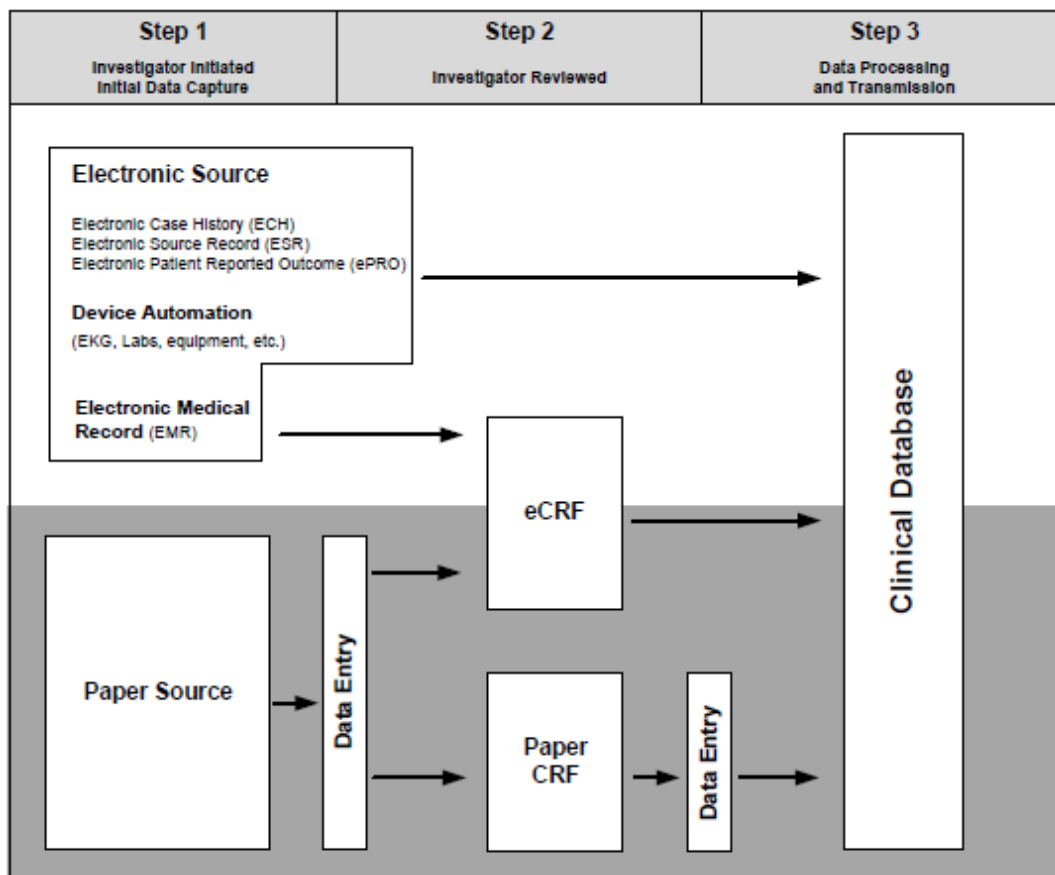


Figure 1

⁸ FDA Form 1572, page 2, “I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.”

Although different from the figure included in the draft guidance, our recommended figure embodies many of the same principles. Notably the idea of the various Tiers for Data Entry, Data Review, and Data Transmission and many of the principles discussed in section III of the draft guidance.

As compared to the existing figure, the recommended figure makes it explicitly apparent that source data can be initially recorded in either electronic or paper formats. In addition, it represents the distinct pathways that data can flow into the clinical database depending on the format of data collection and the capabilities/limitations of available tools. The proposed figure makes reference to the existence of CRFs in both paper and electronic format, and also provides a distinction to permit information documented directly by the investigator electronically (which presupposes that the investigator has reviewed the data as it's being entered) to automatically populate a clinical database. It also points out the steps of manual data entry for paper source documents – an area that the agency has identified as causing substantial problems with data quality and integrity (lines 22 and 23).

The proposed figure also explicitly acknowledges that depending upon the choice of technology, in some cases the source information may be an electronic system (e.g. an EMR) that passes a subset of information into an eCRF as an interim step to populate the clinical database. We point out that this is the explicit intention of current CDISC efforts to demonstrate interoperability between EDC systems and EMR systems. A good example of this type of data would be a subject's medical history, concomitant medications, or laboratory values which are generally available electronically in most EMR environments and which could be transmitted to an eCRF as an interim step prior to the clinical database. Furthermore, the figure also illustrates that some electronic systems can directly populate the clinical database which is the stated intent in line 24.

The proposed figure does not extend the concept of data processing and transmission beyond the clinical database stage. Rather, it is our belief that existing FDA guidance (referred to in lines 28-31) already provides sufficient clarity with respect to the principles for archival, storage, and transmission of data and that those same principles apply to the storage, handling, transmission and archival of electronic source data. We further recognize that there are many potential consumers of source data but respectfully suggest that it is not the purpose of this document to identify all potential end-users of electronic source documents/data so it is sufficient to end the discussion at the point when the source data resides in the clinical database.

We further recommend that the discussion regarding the “review” of data in lines 126-133 be modified to reflect that the review must take place prior to the clinical database being finalized. Standard industry practice, driven both by technological constraints and operational practicalities, is that data entered into an eCRF directly populates the study database. Investigators and sponsors then work together to validate and clean data prior to finalizing the database. Depending on the technology choice, some tools and instruments can, in fact, directly populate the final database with the full involvement/awareness of the investigator without passing through an eCRF as a transitory mechanism. For example, an electronic form, rather than a paper form, completed during the patient encounter could directly feed the database without a secondary and distinct CRF step.

Furthermore, we believe that the proposed figure represents the concepts more simply and with less visual distortion than the many arrows and boxes shown in the existing figure.

5. Tier 1 (Data Entry): As previously mentioned, particularly in this section, we feel the extensive references to information being entered into an eCRF should be stricken and/or modified with the term “electronic source record”.

With respect to lines 159-161, it is our feeling that it is precisely those “newly created” data elements which are the most important to the integrity of the investigational study. It is our opinion that an electronic source record must have an awareness of the protocol. In other words, any system that is intended to capture source electronically, must also be able to demonstrate that the information captured is in exact accordance with the requirements of the protocol. Otherwise, additional stand-alone documentation should be required to substantiate the context in which that new information was created. As an example, every EMR system has the capability to record new information such as a blood pressure. Suppose a protocol specifies that the blood pressure is to be taken after 5 mins sitting down, 10 minutes later while standing, another 10 minutes later while laying down (see lines 230-233). The EMR must be able to capture all of the contextual information which would include the timing of the blood pressure as well as the state of the subject. All of this information is a necessary part of the source documentation and must be fully documented in order to satisfy the full requirement to substantiate that the information was created in compliance with the protocol.

With respect to lines 168-174, consistent with the intent of having an investigator review pertinent information (lines 128-133, Section B – Tier 2 Data Review) it is our recommendation that the values generated automatically by a device are immediately reviewable by a responsible individual prior to the initial recording into the database. This is absolutely technically feasible and should not present a hurdle to the use of automated equipment. For example, a blood pressure machine is connected to a computer, the data is fed into an electronic source record (could be an EMR, some other clinical-trial specific record, or even an EDC system) and the value generated from the machine should be displayed to the individual recording the information prior to transmission into the database. Without the step of an individual reviewing the automatically generated data for accuracy, then all automatically generated data becomes suspect, especially if the equipment is later found to be faulty, out of tolerance or not well maintained. We note that many publicly submitted comments relate to the concern of having an investigator or responsible individual “review and sign off on completed portions of the eCRF” prior to data transmission (lines 128-133). It is our belief that this is a valid request by the agency in the specific case of automatically generated data and that the agency simply needs to clarify this point in the final guidance rather than completely remove the requirement to review data prior to transmission.

Lines 178-184 are extremely important and are made explicitly clear in our proposed figure by showing that paper source must be manually entered into a case report form (paper or electronic) as a mechanism of populating the clinical database. However, in the case where paper source exists, it is absolutely necessary to the integrity of the study for that documentation to be maintained. We strongly support the inclusion, as written, of this section in the final guidance.

Lines 186-194 are made explicitly clear in our proposed figure as shown by having some of the electronic source information feed into an eCRF.

Lines 196-252 we agree with completely as written and especially appreciate the agencies attempt to clarify that data element identifiers can be viewed in multiple ways or with alternative formats (lines

218-221). We believe that, particularly with regard to source information, the additional audit trail related information specified is a necessary requirement to comply with existing GCPs and regulatory guidance. Although many legacy systems do not have the capability to record an expanded audit trail, the agency should not anchor their recommendations to the limitations of previous technologies.

We believe the label “Field in CRF” in Table 1 and Table 2 is inaccurate and should be replaced with “Database Field” because what is shown, and what the audit trail is concerned with, is actually the data values in the final clinical database. The mechanism of populating the database itself should actually be a part of the “Data Element Identifier: Originator” field – which is essentially what is shown in the table (e.g. AB instrument systems, or randomization algorithm). We believe this clarification is necessary for the table to make sense in the context of understanding where the data originated and how it may have changed.

Particularly when talking about changes to source, we strongly agree with the agencies statements regarding modifying/correcting data (lines 238-252). Source data is THE most important information in a clinical study and should not be changed without providing a specific reason for the change. We note that this is entirely consistent with ICH 4.9.3 which governs paper source – the standard for electronic source should be no less stringent. Systems that cannot meet this requirement should not be used.

We strongly agree with the requirement that data elements whose values may change, not auto-populate other than data field other locations in the subject record (lines 257-259). We appreciate that the agency recognizes that certain information can be auto-populated and, in fact, believe that doing so will contribute to the agency’s goal of eliminating data errors that could reasonably be avoided through prudent use of technology.

With respect to lines 288-299, we agree that it is desirable to have a list of originators. We believe that this list of data originators should be maintained and adjusted throughout the trial to account for changes in authorized users – consequently, we recommend deleting the word “prospectively” in favor of “continuously updated”. Consistent with the goal of capturing source electronically, we believe the agency should also include language indicating that these lists can be automatically generated by systems used to capture the information electronically. The phrase, “Each study site should maintain *on site* a list . . .” could potentially be interpreted that the list can only exist “on site” rather than being accessible from a computerized system. As such, we recommend that the words “on site” be deleted from line 288. For example, most systems have a system administration log that includes records of which individuals have access to information, for what time periods, and restrictions on what data they may access. Particularly at a site that performs multiple studies, it is important to know what studies a particular individual is permitted to access. Much of this information is capable of being generated automatically by a systems administrator. Additionally, in the case of an enterprise-wide EMR, it is particularly important to know which individuals or groups have access to information and a detailed understanding is necessary to safeguard the integrity of the data being collected.

The requirement in lines 293-295 that the system capture a unique device identifier, manufacturer, model number and serial number is not practical. We do believe it is important to identify a specific machine, particularly when that machine is automatically generating data; however, the guidance should simply state that it is necessary to identify specific devices and instruments without specifying HOW that identification should be accomplished. For example, many organizations use inventory tracking

systems which give a unique code to each machine – capturing this unique code should be sufficient. Otherwise, if no such system exists, it may be suitable for a site to capture the device number or even the serial number if no other means exists. The higher level issue is that the specific device/instrument should be uniquely identified, but the guidance should not impose the specific way of making that identification.

6. Tier 2 (Data Review): This section correctly points out that the investigator has the responsibility to maintain adequate case histories and to care for the subject’s welfare and safety. We agree with the majority of the public comments on this section which focus on the need to permit data to be transmitted to the clinical database and for the investigator to certify that the subject data in the database is accurate sometime prior to the database being finalized. As we previously pointed out, we believe that the sole exception should be for automatically generated information which should be reviewed by an individual (either at the point the data is generated, as with a blood pressure machine, or at an interim step, as with the use of an eCRF to capture lab data from an EMR) prior to permitting that data to populate the clinical database.

As a further argument against the use of a case report form (paper or electronic), we refer to the same regulations cited in lines 326-340 which explicitly place the onus for source documentation on the investigator. By practice within the industry, a case report form is created, maintained, updated, and controlled by the sponsor. Every sponsor has established procedures to “lock” a CRF after certain events or periods in time. Once locked, the investigative site no longer has access to enter additional information that might become available. Source documents are different – they should never be “locked” or arbitrarily restricted because the sponsor decides that ancillary or supporting data is not necessary; those decisions are the prerogative of the investigator and should not be driven by the sponsor’s particular business practices or preferences. Enshrining the CRF as the central collection point for all electronically collected source data will greatly undermine the responsibility of an investigator to control the type of source documentation required to demonstrate compliance with GCPs, the protocol, and other regulatory guidance. Given the current state of technology, many vendors and sponsors would love to see the CRF as the ‘officially sanctioned’ mechanism to capture source – however, that will have the unintended consequence of removing control and responsibility from the investigator and transferring it to the sponsor by virtue of the manner in which the CRFs are created and deployed. For these reasons we again reiterate our recommendation to use the term “electronic source record” in place of CRF in every instance throughout the document where source data is to be aggregated electronically.

Line 357 should read “The Investigator’s Copy of the Electronic Source Record”.

Line 362-363 is irrelevant in practice because data are constantly being transmitted to the clinical database. We believe this sentence should be eliminated as it adds nothing to ensure the integrity of study data.

Lines 366-368 refer to specific programming language that is commonplace now – XML. However, as history has shown repeatedly, technology evolves and the most efficient data storage and transfer formats and languages change. Rather than explicitly reference the use of XML, we recommend that the sentence read “The source records for each subject, along with the study design and study participation data, may be stored natively in any flexible format that can be easily manipulated or converted into

standard industry formats (XML, PDF, etc) and are compatible with current FDA Study Data Exchange Standards.” This type of open format statement is critical to permitting technology to evolve effectively over time. We note that many types of source data are not necessarily XML – for example imaging files, EKGs, and other data types can be stored in a number of formats. We point out that the agency also acknowledges a wider variety of open format standards and suggest wording similar to that used in other final guidance⁹.

Lines 375-376 assign the responsibility of generating a write-protected copy of the source record to the investigator. We believe that ‘who’ generates the write-protected copy is much less important than that the investigator has unrestricted access to a write-protected copy of the source record.

Furthermore, we believe that this copy needs to be in a human-readable format that mimics the manner in which the data itself was collected, as close as possible. The existing standard is paper – an investigator can easily interpret a paper source document. If the write-protected copy is simply a printout of the database or the XML (to be ridiculous) or a viewer that permits viewing a database, that’s substantially less useful than having a format that can easily be interpreted by the investigator. Without the ability for the investigator, or an FDA auditor, to understand and easily interpret the write-protected copy of the source record, then the benefit of maintaining those records is minimal. In addition to a human-readable copy, a complete write-protected data file should exist which includes the audit trail as well as any modifications/changes to the data. All of this is the responsibility of the investigator and should be permitted to be stored in any number of standard formats.

Lines 380-381 are more appropriately applied to the investigator not the sponsor.

7. Tier 3 (Data Processing and Transmission): We generally concur with the statements in this section.

8. Regulatory Review Collaboration: We agree that, particularly in the early stages of adoption, sponsors should be encouraged to speak with the agency about their intended plans to incorporate various electronic source technologies. However, the protocol (lines 435-438) is not the appropriate place to provide a detailed description of how data will be handled. The ramifications of collecting source data electronically have a much more significant impact on the Data Management Plan and Monitoring Plan. Each of these documents should outline how the electronic source will be collected and reviewed. From an operational perspective, both of these documents are routinely created as part of sponsor SOPs. They are also much more appropriate to focus on the details of electronic source; our concern is that requiring sponsors to discuss electronic source in the protocol, which is a clinically and scientifically focused document, risks diluting the purpose of the protocol and delaying the study unnecessarily as additional technical people are consulted.

Furthermore, it is easily foreseeable that at the time a protocol is finalized that the specific technology decisions have not been made or that the unique technology in place at research sites is unknown. Additionally, the requirements of lines 440-443 are also largely unknown at the time the protocol is finalized because these types of data validation checks are built after the protocol has been finalized and are often added or removed based on lessons learned throughout the study.

⁹ Guidance For Industry – “Part 11, Electronic Records; Electronic Signatures – Scope and Application”; lines 284-296.

Complying fully with the requirement to have detailed discussions of electronic source in the protocol will be a substantial burden to the industry. Amendments to protocol documents must follow strict procedures and are subject to review by multiple groups. In order to limit the costly burden of repeated protocol amendments solely to discuss various data systems it is recommended that the agency remove the requirement that electronic source be discussed in the protocol itself.

We also believe that the guidance as written will ultimately hinder the adoption of electronic source technologies. As previously detailed, investigators have the responsibility to maintain adequate patient case histories – it should be their decision to elect to capture their source documentation electronically regardless of whatever the sponsor may dictate. This situation already exists in many cases where electronic medical records have been implemented – the site chooses to implement an EMR. If the sponsor engages that site, then at least some portion of the source documentation will be found in the EMR regardless of what the sponsor may hope. Consequently, we recommend that language be added that explicitly acknowledges this existing situation and allows sites to have certainty that if they choose to implement electronic source record systems or EMRs with functionality that meets the final guidance that they can do so.

Consequently, we recommend that the guidance include additional language requiring sites who choose to implement means to capture source information electronically to have SOPs governing how and when such systems are to be used, how the data is safeguarded, how the system assures data are collected in compliance with the protocol and GCPs, and all other requirements associated with computerized systems as required by previously issued FDA guidance. In this way, the sites have flexibility to adopt systems and practices that best meet their work practices and to communicate the most relevant aspects of the electronic system to the sponsors who continue to have an obligation to effectively monitor data regardless of what format the site collects it in.

9. Glossary: As previously discussed, change “eCRF” in the definition of Data Originator to be “electronic source record”.

Include the definition of “electronic source record” to be similar to the following:

The compilation of clinical trial-specific subject information initially captured electronically, or subsequently characterized as a Certified Copy, which documents original observations or analyses as required by the study protocol. Such information may be in multiple formats (image files, electronic faxes, electronic forms, eCRFs, etc.) but all of which, together, substantially meet the requirements for a patient case history as outlined in 21 CFR 312.62 and 812.40.

10. Additional Commentary – Cost of Compliance: The mere existence of paper source documents is the single largest cost driver in clinical research today. Publicly available information from the Medidata CRO Contractor product fact sheet¹⁰ shows that site monitoring alone, which largely focuses on source data verification and the examination of other paper records, accounts for approximately one third of the total cost of a clinical trial. In fact, total industry monitoring costs range from \$5 - \$8

¹⁰ CRO Contractor is a comprehensive database of over 5,000 financial contracts between sponsors and CROs for various services. The database uniquely identifies the specific cost components of each contract to provide a benchmark for goods/services pricing. It is the largest database of its type; consequently, it is a good indication of the composition of total study costs; http://www.mdsol.com/sites/default/files/documents/library/brochure/mdsol_cro_contractor.pdf, page 2.

Billion annually – reducing the monitoring burden by eliminating paper source and the associated processes could literally save hundreds of millions. We recognize that the agency must take into account the cost of compliance when issuing any new guidance. We point out these facts to make it clear that the alternative to choosing to comply with the electronic source guidance is to continue to spend money to comply with the existing guidance covering paper source documents. It is our opinion that any argument about the cost of compliance is ill-informed and doesn't reflect an understanding of what the current cost of compliance is.

11. Additional Commentary – Backup Data: Having worked for the last four years specifically on electronic source applications, it is our informed opinion that the very first step to initially record source electronically represents the greatest risk for data loss and corruption.

Any time data is collected electronically there is the possibility of data loss. Once entered into a database, it is relatively easy to establish processes and implement redundant backups to prevent that data from being lost. In this regard, paper is the ultimate backup mechanism. The current workflow, even utilizing electronic data capture systems or EMRs, is for investigators to capture source on paper, then enter that information into the eCRF or EMR database where technology can then be deployed to back up that information in multiple redundant formats.

The challenge with electronic source is the initial recording of information electronically. With ePRO, it is generally well accepted that the information is considered “source” when it hits the database. In the FDA guidance regarding patient reported outcomes, the risk of data loss is explicitly addressed in section F (Specific Concerns When Using Electronic PRO Instruments). The guidance states, “Sponsors also should avoid the following: - The existence of only one database without backup (i.e., risk of data corruption or loss during the trial with no way to reconstitute or verify the data).”

We agree with the generally accepted convention that electronic data “officially” becomes source when it is saved to the database because it is a clear and unambiguous standard which allows for considerable flexibility in designing compliant technologies. With that said, it then becomes a very critical matter as to when and how the information collected as electronic source is recorded in the database as well as at what point in time any backup information is created.

To reiterate the concern, we cite a real-world example of how source might be captured electronically. Suppose a sponsor determines that investigators must use a web-based eCRF to enter data directly into the EDC system during the patient visit¹¹. The investigator must have a connection to the internet that is always available, they access the central study database, select a form and enter the information into a web browser. During the time the information is entered into the browser fields it is not source – it hasn't been committed to the database yet. When finished, the investigator closes and saves the form – this means the data must transit the internet and be saved in the database. Some systems run edit checks on the incoming data before it is saved while other systems record all the information in the database

¹¹ For the moment, ignore the fact that the organizational construct of existing CRF design (including the CDISC CDASH standards) has no relevance to an investigator's natural clinical workflow since CRFs are organized around similar data types whereas traditionally the paper source documents at sites are organized around the clinical activities and workflow. Furthermore, a single clinical visit may require anywhere from 6-10 or more separate CRF forms which would be quite impractical to continue opening and closing given the way current EDC systems operate.

and then run edit checks. Although a small detail, this timing matters because the data could be lost, corrupted or not saved into the database.

Consider how many times you have filled out a web form online, clicked to move to the next page and an error message appears. If you're buying a plane ticket online, it may not matter that you have to re-enter that information again. However, if you are conducting a clinical trial and the data is now gone, then you must redo it which in some cases is not possible or interferes with the integrity of the trial. Furthermore, there is no record that an attempt was made to save data to the database because the failure could have been at the local site internet connection.

The point is that there are an impossible number of problems that can occur which put the electronic source data at greatest risk when it is initially captured. As mentioned, after the point of initial capture there are multiple ways to backup and save that data so it can be restored.

It is technically possible to implement safeguards to back up data during the initial "entry" stage before the data is recorded to the database. Options exist to employ various routines to backup data on the local hard drive, in the memory cache, or elsewhere. It is true, however, that most current systems do not have any means of safeguarding information at the initial data entry stage and would need to develop additional capabilities to address this problem.

We believe that this problem must be explicitly addressed or the risk to the integrity of source data will be too great. We also believe that without explicitly acknowledging the potential for data loss, investigators will be extremely hesitant to adopt any electronic systems because of the risk associated with the information being lost as it's being recorded before it even becomes source.

We also point out that a higher standard for data backup is likely to provoke resistance among established technology vendors who may claim that the need for a backup or redundancy as the data is entered imposes a significant burden or is technically unfeasible. We submit that these technical issues are fully solvable and given the costs associated with the current practices, economically desirable.

For example, within an EMR environment it is certainly possible to implement a secondary and automatic save mechanism to backup entered data on any open screens every 30 seconds prior to that data being officially recorded to the database. This could satisfy the concern that data as it is entered might be lost because the secondary save mechanism could be utilized to recover the data previously entered. We point out that common office productivity tools such as Microsoft Word and Excel utilize automated secondary backups to recover information when an unexpected application glitch occurs.

We strongly reiterate our view that some type of discussion about the need for a secondary backup at the time data is being recorded is necessary for an electronic source system. The standard for comparison is paper – at the time the information is recorded on paper, if my pen runs out of ink, I grab another pen I don't lose what I already wrote.

We believe it is in the interest of assuring the integrity of source data to require a secondary backup. Please consider adding comments addressing this issue to the final guidance.

12. Final Statement: We appreciate that the FDA is taking this step of explicitly clarifying expectations for electronic source. We reiterate our strong belief that the guidance not incorporate terminology that already has an explicitly defined meaning (e.g. case report form or eCRF) in order to define electronic source. We feel the term electronic source record would be a more precise definition and encompass a broader range of electronic source information than simply a case report form structure.

Respectfully submitted,

Dr. Thomas W. Littlejohn, III

Edward S. Seguire, Jr.

Douglas E. Pierce

Appendix A

Differences in Case Report Form and Source Documentation

VISIT 4 : PHYSICAL EXAM - Form Version: 17-Nov-2008 18:25
 Site: Patient: Patient No:
 8245-005

Physical Exam

1.	Enter assessment date if different from visit date	<input type="text"/> / <input type="text"/> / <input type="text"/>
2.	Result	<input type="radio"/> Normal <input checked="" type="radio"/> Abnormal (enter clinically significant findings on MH or AE form)

Figure A.1
Case Report Form Screen Shot

Subj: L B C Subj. #: 0011-532 Date: 04/02/09

Physical Exam

	VI	V4 (Day -1)	V7 (Wk 6) / ET	
BODY SYSTEM	Normal	Abnormal	CHANGE FROM V2 <input type="checkbox"/> NA @ V2	specify the abnormalities
GENERAL APPEARANCE		✓	NA <input checked="" type="checkbox"/> CS <input type="checkbox"/> NCS	overweight
SKIN		✓	NA <input checked="" type="checkbox"/> CS <input type="checkbox"/> NCS	tattoos on rt. arm
HEENT	✓		<input type="checkbox"/> CS <input type="checkbox"/> NCS	
HEART		✓	NA <input checked="" type="checkbox"/> CS <input type="checkbox"/> NCS	irregular heart beat - tachy
LUNGS	✓		<input checked="" type="checkbox"/> CS <input type="checkbox"/> NCS	crackles in lower left chest
ABDOMEN		✓	<input type="checkbox"/> CS <input type="checkbox"/> NCS	
REFLEXES	✓		<input type="checkbox"/> CS <input type="checkbox"/> NCS	
LYMPH NODES	✓		<input type="checkbox"/> CS <input type="checkbox"/> NCS	
NERVOUS SYSTEM	✓		<input type="checkbox"/> CS <input type="checkbox"/> NCS	
EXTREMITIES		✓	<input checked="" type="checkbox"/> CS <input type="checkbox"/> NCS	decoloration of left foot (ulcer) *
OTHER			<input type="checkbox"/> CS <input type="checkbox"/> NCS	

Investigator's Signature: [Signature] Date: 04/02/09

Investigator's Signature: _____ Date: ___/___/___
Co-sign if Necessary

* accident at work -
 EA treatment

Figure A.2
Paper Source Document of Physical Exam