

Comments on Draft Guidance for Industry: Computerized Systems Used in Clinical Trials

General comments:

- 1) We support and agree with the Agency's review and revision of this guidance. The Agency's efforts to bring this guidance in line with the Part 11 Scope and Application Guidance are appreciated.
- 2) We believe that further clarification of the expectations for Investigator Sites, Contract Research Organizations (CROs) and Sponsors in relation to the use of computerized systems would be helpful. More specifically, clarify that clinical investigators are responsible for the validation and documentation of their computerized systems used in the clinical environment for source data and that sponsors/CROs are responsible for the validation and documentation of their computerized systems supplied to the clinical environment for CRF and patient diary information. Consider the example of a computerized system purchased and used by a physician's office to collect information on both patients and clinical trial subjects and acknowledge that Hospital Medical Records systems are out of scope.
- 3) We believe the use of standard wording would provide additional clarity throughout the guidance. For instance, replace "firm" with "sponsor company" and expanding "site" to "investigator site". Use of the terms employees, staff, personnel and individuals should specify whether they refer to investigator sites, CROs or sponsor companies.

Specific comments, annotated to each section of the draft guidance:

1) Section II. Background

Section II states instruments in analytical laboratories are not in the scope of this guidance. With the increasing association of computers and instruments (i.e. computerized instruments), the distinction between instrument and computerized system becomes less distinct. We ask the Agency provide a consistent definition of instruments versus computerized systems.

2) Section III. General Principles

Items 1 and 2 recommend documenting in the study protocol the steps at which a computerized system will be used and identifying what software and hardware are used in those systems. Much of this information will not be known at the time of protocol development. Also, during the course of a lengthy clinical trial, the information concerning computerized systems may frequently change. We agree with the Agency's recommendation to document this information; however the protocol is not the appropriate place to do so.

Item 5 refers to retention of records by the investigator site and recommends retaining either the original source document or a certified copy of the source document to assist in meeting regulatory requirements. Additionally, Item 6 defines when the electronic record is the source document. A common approach for electronic data capture (EDC) in clinical trials is the "thin client (web browser) approach". In this method of EDC, software, forms and data are stored on a central server and accessed through a secure browser connection via the internet. Typically, nothing would reside at the investigator site. We suggest that Item 5 be expanded to include access to and viewing of source documents at the investigator site by means of a secure web browser as acceptable.

Item 8 indicates that information regarding each individual subject be attributable to that subject, while the definition of Attributable Data includes traceability to individuals responsible for observing and recording the data. We suggest changing “attributable to” to “associated with”.

3) Section V. Standard Operating Procedures

In line 541, a user manual is included as an associated document in the definition of Computerized System. Line 137 includes SOPs for site documentation, but does not address user manuals. In the case of a sponsor-provided system at an investigator site, current industry standard is to provide a user manual covering key topics such as system set up/installation, data collection and handling, and alternative recording methods. If the investigator owns and uses a system that is not study specific, such as one used to capture source notes, then the procedures listed in this section would apply. We suggest extending the scope of this section to include user manuals.

4) Section VI. Data Entry: C. Date/Time Stamps

“Daylight Saving Time” is a term typically used in the United States. In the European Union, the term used is “Summertime Period”. We suggest using a more global term. “.....to adjust to seasonal time changes, e.g. Daylight Saving Time”.

5) Section VIII. System Security

Lines 303-305 recommend that procedures and controls be implemented to prevent the data from being altered, browsed, queried or reported via external software applications that do not enter through the protective system software. While steps are routinely taken to restrict access to authorized users and to protect data from unauthorized alteration, data may be browsed, queried or reported by applications such as SQL or Business Objects. We ask for clarification of “protective system software”.

6) Section VIII. System Security

Lines 307-309 recommend a cumulative record of authorized personnel, their titles and a description of their access privileges be kept in the study documentation, accessible at the site. We suggest changing “authorized personnel” to “authorized investigator site personnel”.

7) Section IX. System Dependability

Line 325 implies that clinical investigators' systems used within a trial need to conform to the sponsor's requirements. This would not be possible where source records were held within a central hospital records system, given that the hospital system could be the source of records for trials conducted for several different sponsors. We suggest that investigator sites are responsible for the completeness, accuracy, reliability and consistent intended performance of systems they supply.

8) Section IX. System Dependability

Lines 329-331 recommend that systems documentation be readily available at the investigator site and provide a systems description. For a sponsor provided system, this documentation will typically be maintained at the sponsor. In the instance of a sponsor provided system, an overall system description and the relationships among hardware,

software and physical environment could be provided in a user manual. We suggest recommending that system documentation be readily available for investigator supplied systems and an overall description be available for sponsor provided systems.

9) Section IX. System Dependability: B. Off-the-shelf Software

We suggest the scope of this section be broadened to include investigator sites. We also suggest that copies of validation documents be accepted by the Agency. In addition, lines 401-409 should be removed as this is covered in the preceding text.

10) Section XII. Copies of Records and Record Inspection

We suggest adding the following at line 494, "If application software, operating systems and software development tools involved in the processing of data or records is no longer available, study data requested by the Agency could be reconstructed from available documentation.

11) Section XIII. Certification of Electronic Signatures

This section fails to directly state the responsibility of clinical investigators to submit an electronic signature certification. We request FDA to clarify whether sponsors can certify on behalf of clinical investigators.