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MEMORANDUM

TO: FDA DOCKET 2004D-0440
FROM: CRF INC.
SUBJECT: CLINICAL SYTEMS USED IN CLINICAL TRIALS DRAFT SEPT 2004
DATE: 14 OCTOBER 2004

CRF Inc provides software and services that collect electronic patient reported outcomes for clinical trials. The draft CSUCT guidance document was reviewed from our industry space. The following comments and markup document shows the issues seen as items requiring clarification and revision.

1. Line 16 – Need to add discussion for ePRO devices used in patient’s homes and discussion about the use and status of Application Service Providers (ASP).
2. Line 96 – Need to adjust for “Transient Data Collector” devices which are not good eSource storage locations.
3. Line 96 - The definition of “SYSTEM” should be logical not physical to account for non-traditional computing environments.
4. Line 109 & 214 - “WHY” has been excluded in the past. Not required per P11 final rule preamble IVI.D.para 5 last sentence that states specifically not required. New requirement?
5. Line 122 - If the agency does not intend to enforce P11 can organizations not implement during this timeframe?
6. Line 138 – What does “be available on site” mean? This is not realistic for patient home ePRO devices or investigator sites. There is also no consideration for ASP type services. Need a good definition for “SITE”.
7. Line 184 – This discussion of electronic records should discuss the differences between data and metadata to ensure clarity to users.
8. Line 200 – This paragraph should discuss metadata as it relates to clinical data changes. Are metadata audit trails needed?
9. Line 240 – The term ‘trusted third parties’ is wrong. Each country traces its time to their NIST. In the USA it is time.nist.gov. The term should be changed to “traceable to national standards”.
10. Line 309 – “accessible at the site”. This is not realistic for patient or investigator sites. A good definition for “site” is needed. Same as line 138.
11. Line 317 – Add “and validation” to the end of this line. Owners cannot only evaluate the effects of changes on security, validation is also affected.
12. Line 329 – What is the definition of “site” here. Patient or Investigator?

13. Line 329- 330 – “systems documentation at the site and provide an overall description of the system“ is not practical. Investigators and patients do not need have a full set of documentation nor are they required to understand this information. It would not provide any value added.
14. Line 352 – “Software validation documentation being available at the site”. If the software is purchased per line 385, documentation might not be available. How will this be handled?
15. Line 375 – OFF THE SHELF SOFTWARE – No consideration is given for Application Service Providers. Are they considered “off the shelf”?
16. Line 385 – “OTS software can be assumed validated”. This is an incorrect assumption proven many times. Just because it is made does not mean it is validated!
17. Line 388 – This line implies that on-site vendor audit documents will be available for inspection. Many companies do not share this information. Is the availability of said documentation now an expectation?
18. Line 389 – “Would itself” does this mean sponsor or investigator? It is unclear.
19. Line 389 – Assuming “functional testing” is not always true or might be an informal effort with no objective evidence. The term should also be changed to “System Testing” per IEEE STD 610.12
20. Line 391 – Discusses additional validation efforts. This is typically User Acceptance Testing – UAT and should be required of all purchased software.
21. Line 401 – states that 3 bullets of validation evidence be available. This contradicts with line 388, which states supplier audit evidence, and line 391, which states that UAT is adequate.
22. Line 421 – states re-validation needed on changes that exceed design specs. This might be true for hardware but should never be acceptable for software. Any changes should be tested to ensure continued functionality. This is already a standard industry practice.
23. Line 436 – CONTINGENCY PLANS. This implies that software SOPs include contingency plans. This should be part of the clinical protocol and study SOPs.
24. Line 467 – states “continuing basis, as needed”. This is an unenforceable clause and should be reworded.
25. Line 541 – CERTIFIED COPY. This definition does not account for Data migration, which is a normal part of software lifecycle and long term archiving. These are always validated processes and are not copies as the eSource is moving from one system to another.
26. Line 548 – Direct Entry – This term is not used in industry. The Term should be “eSource” which has been adopted by DIA and CDISC.
27. Line 560 – Original Data – this definition does not account for Transient Data Collection devices. These are portable devices, which are not good eSource boxes. The data is migrated as part of the workflow into central databases which are designated the original data location. See CDISC definition.
28. Line 572 – The term Desing Level Validation is not a common term. I think User Acceptance Testing – UAT would be a better commonly known term.
29. Line 587 – Add the following term – Application Service Provider.
30. Line 587 – Add the following term – Site – Sponsor, ASP, investigator, or patient?

31. Line 587 – Add the following term – eSource Custodian – Trusted 3rd parties holding clinical data. See CDISC term
32. Line 587 – Add the following term. Transient Data – Data that is collected on portable devices and subsequently migrated to eSource databases. See CDISC definition.
33. Line 607 – Reference IEEE STD 610.12 for Software Validation and System Testing definition.
34. Line 607 – Consideration should be given to citing references and definitions in publications from industry groups and consensus standards bodies. Showing only FDA - ICH references implies a “fishbowl” view not in concert with industry.

Feel free to contact me personally, regarding these comments.

Yours truly,

Gregory D. Gogates
VP, Quality Management & Regulatory Affairs

CRF Inc.

1601 Trapelo Rd, Suite 243
Waltham, MA 02451, USA
Tel. +1-781-250-1209
Fax +1-610-222-9347
greg.gogates@crfhealth.com

Guidance for Industry Computerized Systems Used in Clinical Trials

DRAFT GUIDANCE — ERRATUM

On line 563 of this draft guidance, reference is made to Compliance Policy Guide (CPG) # 7130.13. This is incorrect. The CPG number should be 7150.13.

Greg Gogates

Vice President of Quality Management
& Regulatory Affairs



Connected ... for Health

CRF Inc
1601 Trapelo Road, Suite 234
Waltham, MA 02151
Direct: +1 781 250 1209
Fax: +1 610 222 9347
EU Cell: +1 358 40 701 8441
eMail: greg.gogates@crfhealth.com

www.crfhealth.com

← COMMENTS
12 OCT 2004

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

September 2004
Compliance

Revision 1

Guidance for Industry Computerized Systems Used in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Patricia M. Beers Block 301-827-3340.

**U.S. Department of Health and Human Services
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**September 2004
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Revision 1

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Guidance for Industry Computerized Systems Used in Clinical Trials

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TABLE OF CONTENTS

I.	INTRODUCTION.....	2
II.	BACKGROUND	3
III.	GENERAL PRINCIPLES	4
IV.	OVERALL APPROACH TO MEETING PART 11 REQUIREMENTS	5
V.	STANDARD OPERATING PROCEDURES.....	5
VI.	DATA ENTRY	5
	A. Computer Access Controls.....	5
	B. Audit Trails or other Security Measures	6
	C. Date/Time Stamps.....	7
VII.	SYSTEM FEATURES.....	8
	A. Systems Used for Direct Entry of Data	8
	B. Retrieval of Data and Record Retention.....	8
VIII.	SYSTEM SECURITY	8
IX.	SYSTEM DEPENDABILITY	9
	A. Legacy Systems	10
	B. Off-the-Shelf Software.....	10
	C. Change Control.....	11
X.	SYSTEM CONTROLS.....	12
XI.	TRAINING OF PERSONNEL	12
XII.	COPIES OF RECORDS AND RECORD INSPECTION.....	13
XIII.	CERTIFICATION OF ELECTRONIC SIGNATURES	13
	DEFINITIONS	15
	REFERENCES.....	17

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Guidance for Industry¹

Computerized Systems Used in Clinical Trials

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

NEED TO ADD DISCUSSION FOR ePRO devices in patients homes.
NEED TO ADD DISCUSSION ABOUT APPLICATION SERVICE PROVIDERS. -ASP

This document provides guidance about computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained and/or submitted to the Food and Drug Administration (FDA). These data form the basis for the Agency's decisions regarding the safety and effectiveness of new human and animal drugs, biological products, medical devices, and certain food and color additives. Because the data have broad public health significance, they are expected to be of the highest quality and integrity. This guidance document addresses long-standing FDA regulations concerning clinical trial records. It also addresses requirements of the Electronic Records/Electronic Signatures rule (21 CFR part 11).²

Once finalized, this document will supersede the guidance of the same name issued in April 1999. Revisions will make it consistent with Agency policy as reflected in the guidance for industry on *Part 11, Electronic Records; Electronic Signatures — Scope and Application*, which issued in August 2003, and the Agency's international harmonization efforts.³

¹ This guidance has been prepared by an Agency working group representing the Bioresearch Monitoring Program Managers for each Center within the Food and Drug Administration, the Office of Regulatory Affairs, and the Office of the Commissioner.

² Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the requirements of Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in Agency regulations.

³ In August 2003, FDA issued the guidance for industry entitled *Part 11, Electronic Records; Electronic Signatures—Scope and Application* clarifying that the Agency intended to interpret the scope of part 11 narrowly and to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying. In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued *E6 Good Clinical Practice: Consolidated Guidance*.

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32 FDA's guidance documents, including this guidance, do not establish legally enforceable
33 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
34 be viewed only as recommendations, unless specific regulatory or statutory requirements are
35 cited. The use of the word *should* in Agency guidances means that something is suggested or
36 recommended, but not required.

37 38 39 **II. BACKGROUND**

40
41 FDA has the authority to inspect all records relating to clinical investigations conducted under 21
42 CFR 312, 511.1(b), and 812, regardless of how they were created or maintained (e.g., §§ 312.58,
43 312.68, and 812.145). FDA established the Bioresearch Monitoring (BIMO) Program of
44 inspections and audits to monitor the conduct and reporting of clinical trials to ensure that
45 supporting data from these trials meet the highest standards of quality and integrity, and conform
46 to FDA's regulations. FDA's acceptance of data from clinical trials for decision-making
47 purposes depends on FDA's ability to verify the quality and integrity of the data during FDA on-
48 site inspections and audits. To be acceptable, the data should meet certain fundamental elements
49 of quality whether collected or recorded electronically or on paper. For example, data should be
50 attributable, legible, contemporaneous, original⁴ and accurate.

51
52 This guidance addresses how Agency expectations and regulatory requirements regarding data
53 quality might be satisfied where computerized systems are being used to create, modify,
54 maintain, archive, retrieve, or transmit clinical data. Although the primary focus of this guidance
55 is on computerized systems used at clinical sites to collect data, the principles set forth may also
56 be appropriate for computerized systems belonging to contract research organizations, data
57 management centers, and sponsors. Persons using the data from computerized systems should
58 have confidence that the data are no less reliable than data in paper form.

59
60 Computerized medical devices, diagnostic laboratory instruments, and instruments in analytical
61 laboratories that are used in clinical trials are not the subject of this guidance. This guidance
62 does not address electronic submissions or methods of their transmission to the Agency, except
63 to the degree to which these records comply with Part 11.

64
65 The principles in this guidance may be applied where supporting data or source documents⁵ are
66 created (1) in hardcopy and later entered into a computerized system, (2) by direct entry by a
67 human into a computerized system, and (3) automatically by a computerized system.

⁴ FDA is allowing original documents to be replaced by certified copies provided the copies are identical and have been verified as such. (see FDA Compliance Policy Guide # 7130.13). See "Definitions" section for a definition of original data.

⁵ Under 21 CFR 312.62 (b) reference is made to records that are part of case histories as "supporting data;" the ICH E6 *Good Clinical Practice* consolidated guidance uses the term "source documents." These terms describe the same information and have been used interchangeably in this guidance.

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III. GENERAL PRINCIPLES

The Agency recommends the following general principles with regard to computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained and/or submitted to FDA.

1. We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.
2. For each study, we recommend that documentation identify what software and hardware are to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. We also recommend that this documentation be retained as part of the study records. - SIMILAR TO LINE 329
3. We recommend that computerized systems be designed (1) so that all requirements assigned to these systems in a study protocol are satisfied (e.g., data are recorded in metric units, the study blinded) and (2) to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission.
4. It is important to design a computerized system in such a manner so that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems.
5. Under 21 CFR 312.62, 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b) and § 812, respectively, for a period of time specified in these regulations. Retaining the original source document or a certified copy of the source document at the site where the investigation was conducted can assist in meeting these regulatory requirements. It can also assist in the reconstruction and evaluation of the trial throughout and after the completion of the trial.
6. When original observations are entered directly into a computerized system, the electronic record is the source document. - NEED to adjust for "TRANSIENT DATA collector" - systems should mean logical not physical box!
7. Records relating to an investigation must be adequate and accurate in the case of investigational new drug applications (INDs) (see § 312.57 and § 312.62), complete in the case of new animal drugs for investigational use (INADs) (see § 511.1(b)(7)(ii)), and accurate, complete and current in the case of investigational device exemptions (IDEs) (see § 812.140(a) and § 812.140(b)). An audit trail that is electronic or consists of other physical, logical, or procedural security measures to ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred may be needed to facilitate compliance with applicable records regulations. Firms should determine and document the need for audit trails based on a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities. We recommend that audit trails or other security methods used to capture electronic record activities document who made the changes, when, and why changes were made to the electronic record.
8. We recommend that data be retrievable in such a fashion that all information regarding each individual subject in a study is attributable to that subject.

"WHY" has not been required in the past.
PII final rule preamble IVI. D. par 5
LAST sentence states specifically not required

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112 9. To ensure the authenticity and integrity of electronic records, it is important that security
113 measures be in place to prevent unauthorized access to the data in the electronic record
114 and to the computerized system.

115

116 IV. OVERALL APPROACH TO MEETING PART 11 REQUIREMENTS

117

118 As described in the FDA guidance entitled *Part 11, Electronic Records; Electronic Signatures-*
119 *Scope and Application* (August 2003), while the re-examination of part 11 is underway, FDA
120 intends to exercise enforcement discretion with respect to part 11 requirements for validation,
121 audit trail, record retention, and record copying. That is, FDA does not intend to take
122 enforcement action to enforce compliance with these requirements of part 11 while the agency
123 re-examines part 11. Note that part 11 remains in effect and that the exercise of enforcement
124 discretion applies only to the extent identified in the FDA guidance on part 11. Also, records
125 must still be maintained or submitted in accordance with the underlying requirements set forth in
126 the Federal Food, Drug, and Cosmetic Act (Act), the Public Health Service Act (PHS Act), and
127 FDA regulations (other than part 11), which are referred to in this guidance document as
128 *predicate rules*, and FDA can take regulatory action for noncompliance with such predicate
129 rules.⁶

INTERESTING!
IGNORE P11

130

131 Specific details about the Agency's approach to enforcing part 11 can be found in the *Part 11*
132 *Scope and Application* guidance.

133

134

135 V. STANDARD OPERATING PROCEDURES

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137 We recommend that standard operating procedures (SOPs) pertinent to the use of the
138 computerized system be available on site. We recommend that SOPs be established for the
139 following:

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- System Setup/Installation
- Data Collection and Handling
- System Maintenance
- Data Backup, Recovery, and Contingency Plans
- Security
- Change Control
- Alternative Recording Methods (in the case of system unavailability)

← what does "site" mean. Not realistic for home ePRO systems, or investigator sites. No consideration for ASP-type services.

149 VI. DATA ENTRY

151 A. Computer Access Controls

⁶ This term refers to underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the PHS Act, and FDA regulations (other than 21 CFR Part 11). Regulations governing good clinical practice and human subject protection can be found at 21 CFR parts 50, 56, 312, 511, and 812. See Definitions section at the end of this document listing definitions of this and other terms used in this guidance.

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153 To ensure that individuals have the authority to proceed with data entry, data entry systems must
154 be designed to limit access so that only authorized individuals are able to input data
155 (§ 11.10(d)).⁷ Examples of methods for controlling access include using combined identification
156 codes/passwords or biometric-based identification at the start of a data entry session. Controls
157 and procedures must be in place that are designed to ensure the authenticity and integrity of
158 electronic records created, modified, maintained, or transmitted using the data entry system
159 (§ 11.10). Therefore, we recommend that each user of the system have an individual account
160 into which the user logs-in at the beginning of a data entry session, inputs information (including
161 changes) on the electronic record, and logs out at the completion of data entry session.
162

163 We recommend that individuals work only under their own password or other access key and not
164 share these with others. We recommend that individuals not be allowed to log onto the system to
165 provide another person access to the system. We also recommend that passwords or other access
166 keys be changed at established intervals.
167

168 When someone leaves a workstation, we recommend that the SOP require that person to log off
169 the system. Alternatively, an automatic log off may be appropriate for long idle periods. For
170 short periods of inactivity, we recommend that some kind of automatic protection be installed
171 against unauthorized data entry. An example could be an automatic screen saver that prevents
172 data entry until a password is entered.
173

174 B. Audit Trails or other Security Measures

175
176 Section 11.10(e) requires persons who use electronic record systems to maintain an audit trail as
177 one of the procedures to protect the authenticity, integrity, and, when appropriate, the
178 confidentiality of electronic records. As clarified in the *Part 11 Scope and Application* guidance,
179 however, the Agency intends to exercise enforcement discretion regarding specific part 11
180 requirements related to computer-generated, time-stamped audit trails (§ 11.10(e), (k)(2) and any
181 corresponding requirement in § 11.30). Persons must still comply with all applicable predicate
182 rule requirements for clinical trials, including, for example, that records related to the conduct of
183 the study must be adequate and accurate (§§ 312.57, 312.62, and 812.140). It is therefore
184 important to keep track of all changes made to information in the electronic records that
185 document activities related to the conduct of the trial. Computer-generated, time-stamped audit
186 trails or information related to the creation, modification, or deletion of electronic records may
187 be useful to ensure compliance with the appropriate predicate rule. *Should discuss differences
188 IN DATA & METADATA.*

189 In addition, clinical investigators must, upon request by FDA, at reasonable times, permit agency
190 employees to have access to, and copy and verify any required records or reports made by the
191 investigator (§§ 312.68, 511.1(b)(7)(ii) and 812.145). In order for the Agency to review and
192 copy this information, FDA personnel should be able to review audit trails or other documents
193 that track electronic record activities both at the study site and at any other location where
194 associated electronic study records are maintained. To enable FDA's review, information about
195 the creation, modification, or deletion of electronic records should be created incrementally, and
196 in chronological order. To facilitate FDA's inspection of this information, we recommend that

⁷ As FDA announced in the *Part 11 Scope and Application* guidance, we intend to enforce certain controls for closed systems in § 11.10, including § 11.10(d).

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197 clinical investigators retain either the original or a certified copy of any documentation created to
198 track electronic records activities.

199
200 Even if there are no applicable predicate rule requirements, it may be important to have
201 computer-generated, time-stamped audit trails or other physical, logical, or procedural security
202 measures to ensure the trustworthiness and reliability of electronic records. We recommend that
203 any decision on whether to apply computer-generated audit trails or other appropriate security
204 measures be based on the need to comply with predicate rule requirements, a justified and
205 documented risk assessment, and a determination of the potential effect on data quality and
206 record integrity. Firms should determine and document the need for audit trails based on a risk
207 assessment that takes into consideration circumstances surrounding system use, the likelihood
208 that information might be compromised, and any system vulnerabilities. *THIS PARA SHOULD DISCUSS
209 METADATA CHANGES.*

210 If you determine that audit trails or other appropriate security measures are needed to ensure
211 electronic record integrity, we recommend that personnel who create, modify, or delete
212 electronic records not be able to modify the documents or security measures used to track
213 electronic record changes. We recommend that audit trails or other security methods used to
214 capture electronic record activities document who made the changes, when, and why changes
215 were made to the electronic record. *SAME AS LINE 109*

216
217 Some examples of methods for tracking changes to electronic records include:

- 218
- 219 • Computer-generated, time-stamped electronic audit trails.
 - 220 • Signed and dated printed versions of electronic records that identify what, when, and by
221 whom changes were made to the electronic record. When using this method, it is important
222 that appropriate controls be utilized that ensure the accuracy of these records (e.g., sight
223 verification that the printed version accurately captures all of the changes made to the
224 electronic record).
 - 225 • Signed and dated printed standard electronic file formatted versions (e.g., pdf, xml or sgml)
226 of electronic records that identify what, when, and by whom changes were made to the
227 electronic record.
 - 228 • Procedural controls that preclude unauthorized personnel from creating, modifying, or
229 deleting electronic records or the data contained therein.

230 231 C. Date/Time Stamps

232
233 We recommend that controls be put in place to ensure that the system's date and time are correct.
234 The ability to change the date or time should be limited to authorized personnel and such
235 personnel should be notified if a system date or time discrepancy is detected. We recommend
236 that someone always document changes to date or time. We do not expect documentation of
237 time changes that systems make automatically to adjust to daylight savings time conventions.

238 We also recommend that dates and times include the year, month, day, hour, and minute. The
239 Agency encourages establishments to synchronize systems to the date and time provided by
240 trusted third parties. *WRONG TERM! ONLY ONE TRACEABLE TIME SOURCE IN USA,
TIME.NIST.GOV. THE TERM SHOULD BE "TRACEABLE TO NATIONAL
STANDARDS".*

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241 Clinical study computerized systems are likely be used in multi-center trials and may be located
242 in different time zones. For systems that span different time zones, it is better to implement time
243 stamps with a clear understanding of the time zone reference used. We recommend that system
244 documentation explain time zone references as well as zone acronyms or other naming
245 conventions.
246

247

248 **VII. SYSTEM FEATURES**

249

250 The Agency recommends that a number of computerized system features be available to
251 facilitate the collection, inspection, review, and retrieval of quality clinical data. Key features
252 are described here.
253

253

254 **A. Systems Used for Direct Entry of Data**

255

256 We recommend that prompts, flags, or other help features be incorporated into the computerized
257 system to encourage consistent use of clinical terminology and to alert the user to data that are
258 out of acceptable range. We recommend against the use of features that automatically enter data
259 into a field when the field is bypassed.
260

260

261 **B. Retrieval of Data and Record Retention**

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263 FDA expects to be able to reconstruct a clinical study submitted to the agency. This means that
264 documentation, such as that described in the General Principles, Sections III.1, III.2 and III.5,
265 should fully describe and explain how data were obtained and managed and how electronic
266 records were used to capture data. We suggest that your decision on how to maintain records be
267 based on predicate rule requirements and that this documented decision be based on a justified
268 risk assessment and a determination of the value of the records over time. As explained in the
269 Part 11 Scope and Application guidance, FDA does not intend to object to required records that
270 are archived in electronic format; nonelectronic media such as microfilm, microfiche, and paper;
271 or to a standard electronic file format (such as PDF, XML, or SGML). Persons must still comply
272 with all predicate rule requirements, and the records themselves and any copies of required
273 records should preserve their original content and meaning. Paper and electronic record and
274 signature components can co-exist (i.e., as a hybrid system) as long as the predicate requirements
275 (21 CFR parts 50, 56, 312, 511, and 812) are met, and the content and meaning of those records
276 are preserved.
277

277

278 It is not necessary to reprocess data from a study that can be fully reconstructed from available
279 documentation. Therefore, actual application software, operation systems, and software
280 development tools involved in processing of data or records do not need to be retained.

281

282

283 **VIII. SYSTEM SECURITY**

284

285 In addition to internal safeguards built into the computerized system, external safeguards should
286 be put in place to ensure that access to the computerized system and to the data is restricted to

good common sense!

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287 authorized personnel as required by 21 CFR 11.10(d). We recommend that staff be kept
288 thoroughly aware of system security measures and the importance of limiting access to
289 authorized personnel.

290
291 SOPs should be developed and implemented for handling and storing the system to prevent
292 unauthorized access. Controlling system access can be accomplished through the following
293 provisions of part 11 that, as discussed in the part 11 guidance, FDA intends to continue to
294 enforce:

- 295 • Operational system checks (§ 11.10(f));
- 296 • Authority checks (§ 11.10(g));
- 297 • Device (e.g., terminal) checks (§ 11.10(h)); and
- 298 • The establishment of and adherence to written policies that hold individuals
299 accountable for actions initiated under their electronic signatures (§ 11.10(j)).

300
301 The Agency recommends that access to data be restricted and monitored through the system's
302 software with its required log-on, security procedures, and audit trail (or other selected security
303 measures to track electronic record activities). We recommend that procedures and controls be
304 implemented to prevent the data from being altered, browsed, queried, or reported via external
305 software applications that do not enter through the protective system software.

306
307 We recommend that a cumulative record be available that indicates, for any point in time, the
308 names of authorized personnel, their titles, and a description of their access privileges. We
309 recommend that the record be kept in the study documentation, accessible at the site. *what does "site"*
310 *NOT REALISTIC for investigator or patient sites. MEAN?*

311 If a sponsor supplies computerized systems exclusively for clinical trials, we recommend that the
312 systems remain dedicated to the purpose for which they were intended and validated. If a
313 computerized system being used for a clinical study is part of a system normally used for other
314 purposes, we recommend that efforts be made to ensure that the study software be logically and
315 physically isolated as necessary to preclude unintended interaction with nonstudy software. If
316 any of the software programs are changed, we recommend that the system be evaluated to
317 determine the effect of the changes on logical security. *and validation.*

318
319 We recommend that controls be implemented to prevent, detect, and mitigate effects of computer
320 viruses, worms, or other potentially harmful software code on study data and software.

321

322

323 IX. SYSTEM DEPENDABILITY

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325 The Agency recommends that sponsors ensure and document that all computerized systems
326 conform to their own established requirements for completeness, accuracy, reliability, and
327 consistent intended performance.

328

329 We recommend that systems documentation be readily available at the site where clinical trials
330 are conducted and provide an overall description of the computerized systems and the
331 relationships among hardware, software, and physical environment. *- Similar to line 78*

332 *A full set of "systems documentation" includes all SLC deliverable. This is not*
PRACTICAL nor will be understood by "sites"!

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333 As noted in the *Part 11 Scope and Application* guidance, the Agency intends to exercise
334 enforcement discretion regarding specific part 11 requirements for validation of computerized
335 systems. We suggest that your decision to validate computerized systems and the extent of the
336 validation take into account the impact the systems have on your ability to meet predicate rule
337 requirements. You should also consider the impact those systems might have on the accuracy,
338 reliability, integrity, availability, and authenticity of required records and signatures. Even if
339 there is no predicate rule requirement to validate a system, it may still be important to validate
340 the system, based on criticality and risk, to ensure the accuracy, reliability, integrity, availability
341 and authenticity of required records and signatures.
342

343 We recommend that you base your approach on a justified and documented risk assessment and
344 determination of the potential of the system to affect data quality and record integrity. For
345 example, in the case where data are directly entered into electronic records and the business
346 practice is to rely on the electronic record, validation of the computerized system is important.
347 However when a word processor is used to generate SOPs for use at the clinical site, validation
348 would not be important.
349

350 If validation is required, FDA may ask to see the regulated company's documentation that
351 demonstrates software validation. The study sponsor is responsible for making any such
352 documentation available if requested at the time of inspection at the site where software is used.
353 Clinical investigators are not generally responsible for validation unless they originated or
354 modified software.
355

356 **A. Legacy Systems**

*IF the software is purchased per
Line 385, DOCUMENTATION MAY NOT
BE AVAILABLE.*

357
358 As noted in the *Part 11 Scope and Application* guidance, the Agency intends to exercise
359 enforcement discretion with respect to all part 11 requirements for systems that otherwise were
360 fully operational prior to August 20, 1997, the effective date of part 11, under the circumstances
361 described below. These systems are also known as legacy systems. The Agency does not intend
362 to take enforcement action to enforce compliance with any part 11 requirements if all the
363 following criteria are met for a specific system:
364

- 365 • The system was in operation before the part 11 effective date.
- 366 • The system met all applicable predicate rule requirements prior to the part 11 effective date.
- 367 • The system currently meets all applicable predicate rule requirements.
- 368 • There is documented evidence and justification that the system is fit for its intended use.
369

370 If a system has changed since August 20, 1997, and if the changes would prevent the system
371 from meeting predicate rule requirements, part 11 controls should be applied to part 11 records
372 and signatures pursuant to the enforcement policy expressed in the part 11 guidance. Please refer
373 to the *Part 11 Scope and Application* guidance for further information.
374

375 **B. Off-the-Shelf Software**

*NO CONSIDERATION FOR APPLICATION SERVICE
PROVIDERS -*

376
377 While the Agency has announced that it intends to exercise enforcement discretion regarding
378 specific part 11 requirements for validation of computerized systems, persons must still comply

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379 with all predicate rule requirements for validation. We suggested in the guidance for industry on
380 part 11 that the impact of computerized systems on the accuracy, reliability, integrity,
381 availability, and authenticity of required records and signatures be considered when you decide
382 whether to validate, and noted that even absent a predicate rule requirement to validate a system,
383 it might still be important to validate in some instances.

385 For most off-the-shelf software, the design level validation will have already been done by the
386 company that wrote the software. Given the importance of ensuring valid clinical trial data,
387 FDA suggests that the sponsor or contract research organization (CRO) have documentation *USUALLY NOT*
388 (either original validation documents or on-site vendor audit documents) *shared with*
389 validation by the vendor and would itself have performed functional testing (e.g., by use of test *FDA!*
390 data sets) and researched known software limitations, problems, and defect corrections. Detailed
391 documentation of any additional validation efforts performed by the sponsor or CRO will
392 preserve the findings of these efforts. *MEANING SPONSOR*
IN CORRECT TERM. "SYSTEM

393 *TESTING" WOULD BE PREFERRED.*
THIS MEANS UAT + SHOULD BE REQ'D. OF VENDOR?
394 In the special case of database and spreadsheet software that is: (1) purchased off-the-shelf, (2)
395 designed for and widely used for general purposes, (3) unmodified, and (4) not being used for
396 direct entry of data, the sponsor or contract research organization may not have documentation of
397 design level validation. FDA suggests that the sponsor or contract research organization perform
398 functional testing (e.g., by use of test data sets) and research known software limitations,
399 problems, and defect corrections.

401 In the case of off-the-shelf software, we recommend that the following be available to the *This conflicts*
402 Agency on request: - *This implies a full set of vendor val docs?* *with line 391 which*
403 *states only UAT is needed*

- 404 • A written design *or incorrect, this should state functional.* specification that describes what the software is intended to do and how
405 it is intended to do it;
- 406 • A written test plan based on the design specification, including both structural and
407 functional analysis; and
- 408 • Test results and an evaluation of how these results demonstrate that the predetermined
409 *FUNCTIONAL* design specification has been met.

410 Additional guidance on general software validation principles can be found in FDA's guidance
411 entitled *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*.

C. Change Control

415 FDA recommends that written procedures be put in place to ensure that changes to the
416 computerized system, such as software upgrades, including security and performance patches,
417 equipment or component replacement, or new instrumentation, will maintain the integrity of the
418 data and the integrity of protocols. We recommend that the effects of any changes to the system
419 be evaluated and a decision made regarding whether, and if so, what level of validation activities
420 related to those changes would be appropriate. We recommend that validation be performed for
421 those types of changes that exceed previously established operational limits or design
422 specifications. Finally, we recommend that all changes to the system be documented.

*THIS STATEMENT ONLY VALID FOR HARDWARE. ALL SOFTWARE CHANGES
REQUIRE RE-VALIDATION EFFORTS AS A STANDARD PRACTICE*

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X. SYSTEM CONTROLS

The Agency recommends that appropriate system control measures be developed and implemented.

- Software Version Control

We recommend that measures be put in place to ensure that versions of software used to generate, collect, maintain, and transmit data are the versions that are stated in the systems documentation.

- Contingency Plans ← *IS THIS A SOFTWARE DOCUMENTATION EFFORT OR SHOULD IT BE INCLUDED AS PART OF THE PROTOCOL DOCUMENTATION?*

We recommend that written procedures describe contingency plans for continuing the study by alternate means in the event of failure of the computerized system.

- Backup and Recovery of Electronic Records

When electronic formats are the only ones used to create and preserve electronic records, the Agency recommends that backup and recovery procedures be outlined clearly in SOPs and be sufficient to protect against data loss. We also recommend that records be backed up regularly in a way that would prevent a catastrophic loss and ensure the quality and integrity of the data. We recommend that records be stored at a secure location specified in the SOPs. Storage is typically offsite or in a building separate from the original records.

We recommend that backup and recovery logs be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.

Firms that rely on electronic and paper systems should determine the extent to which backup and recovery procedures are needed based on the need to meet predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on data quality and record integrity.

XI. TRAINING OF PERSONNEL

Under 21 CFR 11.10(i), firms using computerized systems must determine that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks.

The Agency recommends that training be provided to individuals in the specific operations with regard to computerized systems that they are to perform. We recommend that training be conducted by qualified individuals on a continuing basis, as needed, to ensure familiarity with the computerized system and with any changes to the system during the course of the study.

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470 We recommend that employee education, training, and experience be documented.
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XII. COPIES OF RECORDS AND RECORD INSPECTION

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475 FDA has the authority to inspect all records relating to clinical investigations conducted under 21
476 CFR Parts 312 and 812, regardless of how the records were created or maintained (21 CFR
477 312.58, 312.68, and 812.145). Therefore, you should provide the FDA investigator with
478 reasonable and useful access to records during an FDA inspection. As noted in the *Part 11,*
479 *Electronic Records; Electronic Signatures- Scope and Application* guidance, the Agency intends
480 to exercise enforcement discretion with regard to specific part 11 requirements for generating
481 copies of records (§ 11.10(b) and any corresponding requirement in § 11.30). We recommend
482 that you supply copies of electronic records by:

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- Producing copies of records held in common portable formats when records are maintained in these formats

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- Using established automated conversion or export methods, where available, to make copies available in a more common format (e.g., pdf, xml, or sgml formats)

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Regardless of the method used to produce copies of electronic records, it is important that the copying process used produces copies that preserve the content and meaning of the record. For example, if you have the ability to search, sort, or trend records, copies given to FDA should provide the same capability if it is reasonable and technically feasible. FDA expects to inspect, review, and copy records in a human readable form at your site, using your hardware and following your established procedures and techniques for accessing records.

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We recommend you contact the Agency if there is any doubt about what file formats and media the Agency can read and copy.

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XIII. CERTIFICATION OF ELECTRONIC SIGNATURES

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As required by 21 CFR 11.100(c), persons using electronic signatures to meet an FDA signature requirement must, prior to or at the time of such use, certify to the Agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

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As set forth in § 11.100(c)(1), the certification must be submitted in paper, signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, Maryland 20857. The certification is to be submitted prior to or at the time electronic signatures are used. However, a single certification can be used to cover all electronic signatures used by persons in a given organization. This certification is created by persons to acknowledge that their electronic signatures have the same legal significance as their traditional handwritten signatures. See the following example of a certification statement:

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515 Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations,
516 this is to certify that [name of organization] intends that all electronic
517 signatures executed by our employees, agents, or representatives, located
518 anywhere in the world, are the legally binding equivalent of traditional
519 handwritten signatures.

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DEFINITIONS

The following is a list of definitions for terms as they are used in, and for the purposes of, this guidance document.

Attributable Data: Attributable data are those that can be traced to individuals responsible for observing and recording the data. In an automated system, attributability could be achieved by a computer system designed to identify individuals responsible for any input.

Audit Trail: An *audit trail* is a secure, computer generated, time-stamped electronic record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record.

Certified Copy: A copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original. *NEED TO DISCUSS MIGRATION OF DATA FROM ONE SYSTEM TO ANOTHER. IS THIS ALSO A COPY?*

Computerized System: A *computerized system* includes computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical trial.

← should be called e Source.
Direct Entry: Recording data where an electronic record is the original capture of the data. Examples are the keying by an individual of original observations into the system, or automatic recording by the system of the output of a balance that measures subject's body weight.

Electronic Record: Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Electronic Signature: A computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

Original data: *Original data* are those values that represent the first recording of study data. *NEED TO ACCOUNT FOR TRANSIENT DATA COLLECTORS!*
FDA is allowing original documents and the original data recorded on those documents to be replaced by certified copies provided the copies are identical and have been verified as such. (see FDA Compliance Policy Guide # 7130.13)

Predicate rule: This term refers to underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the PHS Act, and FDA regulations (other than 21 CFR part 11). Regulations governing good clinical practice and human subject protection can be found at 21 CFR parts 50, 56, 312, 511, and 812.

Software Validation: Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses and that the particular

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user Acceptance testing

572 requirements implemented through the software can be consistently fulfilled. ~~Design level~~
573 ~~validation~~ is that portion of the software validation that takes place in parts of the software life
574 cycle before the software is delivered to the end user.

575
576 **Source Documents:** Original documents and records including, but not limited to, hospital
577 records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation
578 checklists, pharmacy dispensing records, recorded data from automated instruments, copies or
579 transcriptions certified after verification as being accurate and complete, microfiches,
580 photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at
581 the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical
582 trial.

583
584 **Transmit:** *Transmit* is to transfer data within or among clinical study sites, contract research
585 organizations, data management centers, or sponsors. Other Agency guidance covers
586 transmission from sponsors to the Agency.

587

ASP: - Application service providers. Third parties who create, host, and manage clinical software applications.

Site: - Sponsor or ASP? Investigator or patient?

eSource Custodian - TRUSTED 3rd parties holding clinical data for investigators or sponsors. (see CDISC def.)

TRANSIENT DATA - Data that is collected on portable devices and subsequently migrated to eSource databases. (see CDISC def.)

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607
IEEE STD 610.12 for software validation definition in line 570
IEEE STD 610.12 for SYSTEM TESTING DEFINITION IN LINE 389

CONSIDERATION SHOULD BE GIVEN TO CITING REFERENCES AND
DEFINITIONS IN PUBLICATIONS FROM INDUSTRY GROUP AND
CONSENSUS STANDARDS BODIES. SHOWING REFERENCES FROM ONLY
FDA SOURCES IMPLIES "FISHBOWL" THINKING NOT IN CONCERT WITH
INDUSTRY.