

Guidance for Industry

Electronic Source Documentation in Clinical Investigations

DRAFT GUIDANCE

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Electronic Source Documentation in Clinical Investigations

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1 **Guidance for Industry¹**
2 **Electronic Source Documentation in Clinical Investigations**
3

4 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current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

10
11
12 **I. INTRODUCTION**
13

14 This document provides guidance to sponsors, contract research organizations (CROs), data
15 management centers, and clinical investigators on capturing, using, and archiving electronic data
16 in FDA-regulated clinical investigations. This guidance is intended to ensure the reliability,
17 quality, integrity, and traceability of electronic source data and source records maintained at the
18 site for FDA inspection.

19
20 This guidance is intended to promote the capture of source data in electronic form, which will
21 help to:

- 22 • eliminate unnecessary duplication of data,
- 23 • reduce the opportunity for transcription errors,
- 24 • promote the real-time entry of electronic source data during subject visits, and
- 25 • ensure the accuracy and completeness of data (e.g., through the use of electronic prompts
26 for missing or inconsistent data).

27
28 This guidance is intended to be used together with the guidances for industry ² entitled:

- 29 • *Computerized Systems Used in Clinical Investigations*
- 30 • *Part 11, Electronic Records; Electronic Signatures – Scope and Application*
- 31 • *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*
32

33 FDA's guidance documents, including this guidance, do not establish legally enforceable
34 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
35 be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Office of Critical Path Programs, the Good Clinical Practice Program, and Bioresearch Monitoring Program Managers for the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health at the Food and Drug Administration.

² FDA guidances are available on FDA's Web page at www.fda.gov/RegulatoryInformation/Guidances/default.htm. FDA guidances are issued and updated regularly. We recommend you check the Web site to ensure that you have the most up-to-date version of a guidance.

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36 cited. The use of the word *should* in Agency guidances means that something is suggested or
37 recommended, but not required.

38
39

II. BACKGROUND

40

41
42 The initial documentation of data in a clinical study is considered *Source* documentation or
43 *Source* data. The originator, or recorder, may document the data either on paper or
44 electronically. Source data documented in paper format (paper source document) is a tangible
45 document that can be physically located at a clinical study site and readily available for
46 inspection and copying by FDA investigators.

47

48 With the increasing use of computerized systems in clinical studies, it is common to find at least
49 some source data documented electronically (eSource document). Common examples include
50 clinical data initially documented in electronic health records maintained by hospitals and
51 institutions; electronic case report forms (eCRF), which are increasingly being used by clinical
52 study sponsors; electronically generated laboratory reports; electronic medical images from
53 devices; and electronic diaries provided by study subjects. The use of eSource documentation is
54 of great value in the conduct of clinical studies. However, unlike paper source documents,
55 eSource documents and data can be easily copied, transferred to other computerized systems or
56 devices, changed, or deleted without obvious evidence of these events.

57

58 Access to source documents and source data is essential to inspection and review of clinical
59 studies and inspection of clinical study sites. Verification of source data is necessary to confirm,
60 among other things, the participation of subjects and to detect omissions, transcription errors,
61 alterations in data, or falsification of data. When paper source documents are available for
62 review, tracing of data in paper-based studies can be performed easily. However, when source
63 data are electronic, the data are traced through complex data capture, transmission and archival
64 processes.

65

66 This guidance recommends practices that will help ensure that electronic source data are
67 accurate, legible, original, attributable (e.g., user name and password), and contemporaneously
68 entered; and meet the regulatory requirements for recordkeeping and record retention.³

69

70 This guidance discusses the following specific topics related to electronic source data:

71

72

- The identification of the *data element* as the basic unit of information in the eCRF
- The description of the source of each data element

³ Investigators are required to maintain adequate and accurate case histories that record all observations and other data pertinent to an investigation under 21 CFR 312.62(b) and 21 CFR 812.140(a). Investigators of device studies must maintain the study records during the investigation and for a period of two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application. 21 CFR 812.140(d). Investigators of drug studies must retain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. 21 CFR 312.62(c).

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- 73 • Information about the electronic creation, modification, transmission, and storage of
- 74 source data and documents
- 75 • Investigator responsibilities with respect to reviewing and archiving data
- 76 • Transmission of data to the sponsor and/or other designated parties
- 77 • Preservation of data integrity

78
79

III. ELECTRONIC SOURCE DOCUMENTS AND SOURCE DATA

80
81

82 FDA regulations define an *electronic record* as any combination of text, graphics, data, audio,
83 pictorial, or other information represented in digital form that is created, modified, maintained,
84 archived, retrieved, or distributed by a computer system (21 CFR 11.3(b)(6)).

85

86 The terms *eSource* documents and *eSource* data are not defined in FDA’s regulations. For the
87 purpose of this guidance, the terms *eSource documents* and *eSource data* are used to describe
88 source documents and source data for which the original record and certified copies⁴ are initially
89 captured electronically. *eSource* documents and *eSource* data can come from a variety of
90 activities and places. For example, study personnel may perform a direct entry of clinical data
91 into a computerized study database. *eSource* data may be collected from a subject’s electronic
92 health record, which is maintained by clinical study staff. *eSource* data also can come from an
93 electronic diary, maintained by a study subject or from an automated instrument that records and
94 stores a subject’s biological readings.

95

96 The eCRF is a vehicle used to assemble all the data from different electronic- and paper-based
97 systems and makes it possible to capture and organize these diverse data in a manner that
98 satisfies the study protocol and that enables the data to be systematically reviewed and analyzed
99 by investigators, other authorized parties, and FDA (e.g., during FDA inspections).

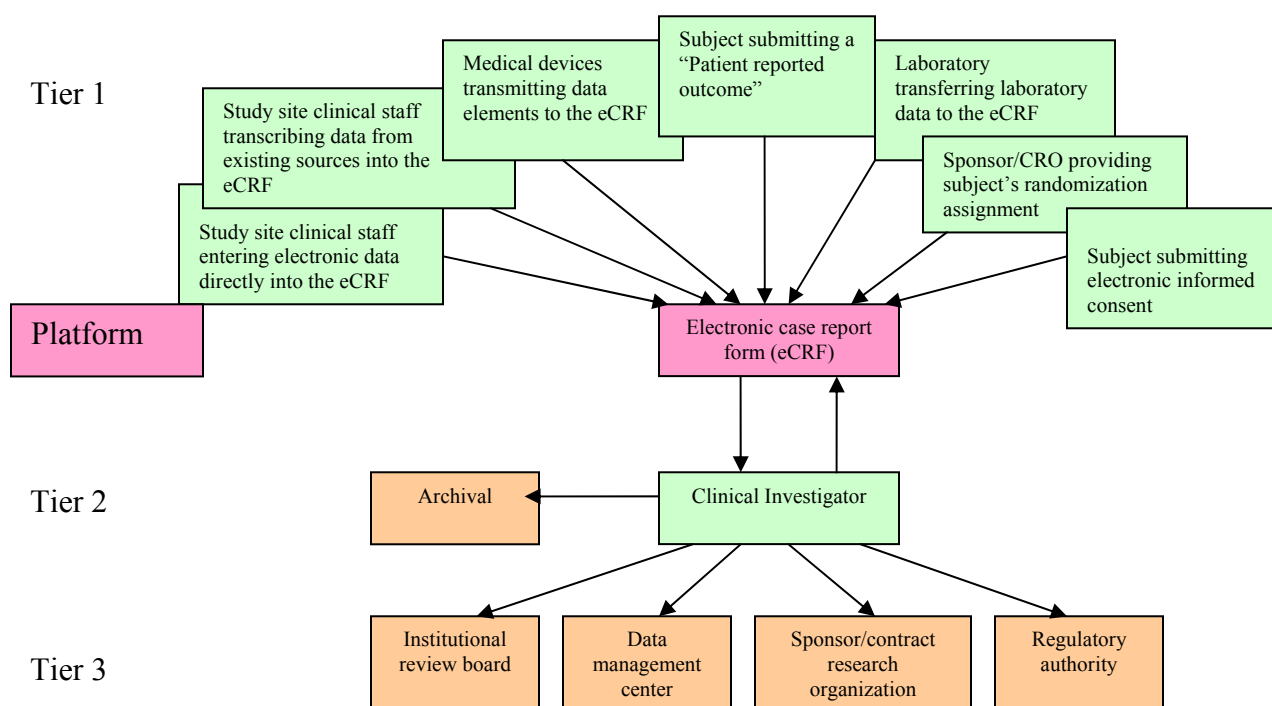
100

101 Figure 1 depicts one example of how data might flow in a clinical study from the point of data
102 entry into an eCRF, and eventually into a tabulation prepared by the sponsor and submitted to
103 FDA in support of a marketing application. In figure 1, three tiers of data management are
104 identified: Tier 1-Data Entry; Tier 2-Data Review; and Tier 3-Data Processing and Transmission.
105 As illustrated in figure 1, data from paper-based or computer-based systems can ultimately be
106 preserved in the eCRF as electronic data.

⁴ See Glossary of Terms in this document.

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110 **Figure 1: Assembly and processing of data elements using the eCRF as a platform**

111
112 Tier 1 (Data Entry): Tier 1 represents examples of various categories of data *originators*, those
113 responsible for creating the data elements in a clinical study (e.g., the clinical investigator, study
114 site clinical staff, medical devices, and subjects; see section III.A of this document for further
115 discussion). Original observations can be entered directly into the eCRF or transmitted to the
116 eCRF from various locations, devices, or instruments. Source data could be collected and
117 documented initially on paper and transcribed into an electronic system or documented initially
118 electronically (i.e., direct entry).

119
120 Associated with each of these categories is a list of authorized data originators (e.g., the category
121 Patient Reported Outcome may contain a list of all the subjects providing a patient reported
122 outcome). Each of these authorized data originators would have an individual identifier (e.g.,
123 user name and password) that enables him/her to electronically enter specific data elements into
124 the system.

125
126 Tier 2 (Data Review): Once the data elements have been integrated into an eCRF, the clinical
127 investigators, who are ultimately responsible for conducting or personally supervising the
128 conduct of a study,⁵ can review the eCRF. Investigators thus have the opportunity to review
129 completed portions of the eCRF, to query the originator prior to transmission to the sponsor and

⁵ See 21 CFR 312.3(b) and 812.3(i).

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130 other parties regarding data elements that raise concerns, and ensure that any relevant clinical
131 issues raised by the data are addressed. Once investigators have reviewed and signed off on
132 completed portions of the eCRF for a study subject, the data can be archived and transmitted to
133 the parties in Tier 3.⁶

134

135 Tier 3 (Data Processing and Transmission): These are parties responsible for study data
136 management who may receive the data once the investigators have signed off (e.g., the
137 institutional review board, sponsor).

138

139 Certain individuals can operate at more than one Tier. For example, the investigator could enter
140 data at Tier 1 as *study site clinical staff*, view subject data and sign off on eCRFs at Tier 2 as
141 *investigators*, and analyze and report data as an *investigator/sponsor* at Tier 3.

142

143 The following sections describe in more detail the data that are captured or managed at each Tier
144 level.

145

A. Tier 1 - Data Entry⁷

147

1. Data Elements

149

150 A data element in an eCRF represents a single observation associated with a subject in a clinical
151 study. Examples include birth date, white blood cell count, pain severity measurement, or other
152 clinical observation made and documented during a study.

153

154 For each data element provided on a subject in a clinical study, there is an originator responsible
155 for its entry into the eCRF (see section III.A.2 of this document).

156

a. New Data Elements Created by Authorized Originators

158

159 Many data elements in a clinical study are newly created at a study visit and may be entered
160 directly into the eCRF by an authorized data originator (e.g., blood pressure, weight,
161 temperature, pill count, resolution of a symptom or sign). FDA may sometimes request other
162 documents to corroborate a newly created data element entered directly into the eCRF by an
163 authorized originator. For example, in an initial visit, an investigator may ask a subject about
164 underlying illnesses such as diabetes, and proceed to enter *diabetes* in a section on underlying
165 illnesses. FDA may request a hospital record to review for evidence of blood glucose testing or
166 the use of anti-diabetic agents to corroborate a diagnosis of diabetes.

167

⁶ Under exceptional circumstances, a protocol may require the blinding of an investigator to specific data elements. For example, a measurement of urine osmolality could effectively unblind the treatment allocation for an osmotic diuretic. In such protocol-specified situations, a party in Tier 1 would be able to transmit a data element directly to a party in Tier 3 without the investigator's sign off.

⁷ Consistent with the principles of the International Conference on Harmonisation, "E6 Good Clinical Practice: Consolidated Guidance," which is available on the FDA guidance Web page.

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168 The accuracy of data elements that are transferred automatically from a medical device or
169 instrument to the eCRF (e.g., a laboratory measurement of hemoglobin, an EKG, or an
170 automated measurement of blood pressure) depends on the ability of the equipment to record and
171 transmit data from the device or instrument to the eCRF. FDA may ask the sponsor and/or
172 investigator during an inspection for information on the reliability and integrity of the software
173 and equipment used to record and transmit the data element, and the ability of the software to
174 ensure that data elements are entered for the correct subject.

175

176 b. Transcription of Data Elements from Other Source Documents

177

178 Data elements that are transcribed by an individual from a source document, such as a laboratory
179 report or hospital record, into an eCRF should carry a data element identifier reflecting the
180 originator responsible for entering the transcribed data element. The source documents related to
181 the study and from which the data elements are transcribed must be maintained and available to
182 an FDA inspector if requested (e.g., an original or verified copy of a laboratory report;
183 instrument printout; progress notes of the physician; the study subject's hospital chart(s), and
184 nurses' notes). See 21 CFR 312.62(b), 312.68, 812.140(a)(3), and 812.145(b).

185

186 Other data elements, such as those originating in an electronic health record, can populate the
187 eCRF automatically. In such situations, the electronic health record would be identified as the
188 source of the information and must be made available for review during an FDA inspection. The
189 sponsor and/or investigator may also be asked during the inspection to provide information on
190 the ability of the software to transfer accurate and complete data from the electronic health
191 record into the eCRF.⁸ Algorithms for data extraction should be described in the study protocol
192 or in another document that includes data management details. For example, some patient data
193 in the electronic health record, such as concomitant medications, may change with time. The
194 procedure for selecting the appropriate data element should be described.

195

196 2. *Data Element Attributes and Data Element Identifiers*

197

198 a. Data Element Attributes

199

200 *Data element attributes* are pieces of electronic information that are linked to a data element
201 (e.g., for the data element "hemoglobin", the attributes might include the value=13gm/dl, date of
202 the observation=February 12, 2009, observation type=laboratory test, data type=numeric), which
203 ensure the correct electronic processing of the data element. They also provide information on
204 the source of data elements.⁹

205

206 b. Data Element Identifiers

207

208 *Data element identifiers* are those attributes that identify:

⁸ Ibid.

⁹ See the Study Data Exchange standards on the FDA Data Standards Council Website for the technical details on data element attributes at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.

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- 213
- the originators of data elements, including those entered manually (e.g., by the investigator), and automatically (e.g., from a device or instrument);
 - the date and time the data elements are entered into the eCRF; and
 - the study subject to which the data elements belong.

214 These allow FDA reviewers and investigators to examine the audit trail of the data.

215

216 c. Display of Data Element Identifiers

217

218 Although it is not necessary to automatically display the data element identifiers wherever data
219 elements appear, the system should include a functionality that enables the user to reveal or
220 access the data element identifiers related to each element (e.g., by cursor placement over the
221 element, and/or a view mode displaying the data element together with its identifiers).

222

223 The following table gives examples of data elements and corresponding data element identifiers.

224

225

Table 1. -- Example of Data Elements and Data Element Identifiers*

Field in eCRF	Data Element	Data Element Identifier: Originator	Data Element Identifier: Date and Time	Data Element Identifier: Study Subject
Patient ID#	AD0012	Randomization algorithm in central computer	June 1 st , 2008/3.00 pm	AD0012
Sex	male	Investigator Dr R Smith	June 1 st , 2008/10.53 am	AD0012
Age	25 years	Investigator Dr R Smith	June 1 st , 2008/10.53 am	AD0012
Hemoglobin	15.3 gm/dl	Co-op labs	June 2 nd , 2008/noon	AD0012
**Date and time blood was drawn for hemoglobin determination	June 1 st , 2008/9.23 am	Investigator Dr R Smith	June 1 st , 2008/10.53 am	AD0012
Radiological report	Right upper lobe consolidation	Dr P Brown, Radiological Associates	June 1 st , 2008/4.12 pm	AD0012
Blood pressure	124/88	AB instrument systems	June 1 st , 2008/10.20 am	AD0012
Concomitant medications	***Lasix 40mg QD	Investigator Dr R Smith	June 1 st , 2008/10.53 am	AD0012

226

227 * FDA recommends that clinical data be entered electronically by study site personnel at the time of the
228 subject visit to avoid transcription from unnecessary paper records.

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230 ** The timing of certain data elements may be important (e.g., the precise time at which sample was
231 drawn). In this case, the time that the sample was drawn should be obtained as a separate data element
232 since the data element identifier indicates the time that the data element was entered into the computer,
233 not the time the sample was drawn.

234
235 *** To verify this transcribed data, FDA may request other existing documentation such as a prescription
236 record or pharmacy record.

237

238 3. Modifications and Corrections

239

240 Modified and/or corrected data elements should carry new data element identifiers, reflecting the
241 date, time, and originator of the change. Both the modified data elements and their data element
242 identifiers should be write-protected. A text field describing the reason for the change and the
243 relationship to the original record (e.g., append, replace) should be added.

244

245 The original data element with its original data element identifiers should be preserved and
246 available for review by FDA investigators.

247

248 The following table gives an example of a modification to a data element. This information
249 would also apply to correcting a data element.

250

251

Table 2. – Example of Modification/Correction

Field in eCRF	Data Element	Data Element Identifier
Hemoglobin	12.3gm/dl	<u>Modified by:</u> Investigator assistant Dr B Green/July 7 th , 2008/9.00 am/AD0012 <u>Reason:</u> Data error reported by Co-op labs July 6 th 2008 due to standardization problem; sample was retested <u>Original data (write-protected automated carryover):</u> Hemoglobin 15.3gm/dl (Co-op labs/June 2 nd , 2008/noon)/AD0012

252

253 4. Repeated Appearance of the Same Data Element in an eCRF

254

255 Occasionally a data element may appear more than once in the eCRF. A data element can
256 automatically populate more than one appropriate location in the eCRF where it is meant to
257 appear. However, data elements should not automatically populate multiple fields in the eCRF
258 where the data may change. For example, a subject's weight measurement should not
259 automatically populate later visits in the case report form since the weight may change over time.

260

261 5. Electronic Prompts to Ensure Accuracy and Completeness of Data

262

263 FDA encourages the use of electronic prompts in the eCRF to minimize errors and omissions at
264 the time of data entry. Prompts may be designed to alert the originator to missing data, data

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265 inconsistencies, inadmissible values, and to request additional data where appropriate (e.g., by
266 generating an adverse event report form triggered by a critical laboratory result).

267

268 6. *Originators of Data Elements*

269

270 *Originators* of data elements can include site clinical staff entering data into a computerized
271 system or medical devices automatically populating specific data fields in the eCRF. Examples
272 of data originators include but are not limited to:

- 273 • Investigators or authorized study site clinical staff responsible for interviewing study
274 subjects (The data elements they provide might be obtained either by observation of
275 subjects or by review of patient records.)
- 276 • Biomedical devices (e.g., a blood pressure machine or EKG machine)
- 277 • Automated laboratory reporting systems
- 278 • Imaging facilities
- 279 • Consulting services (e.g., a radiologist reporting on a CT scan)
- 280 • Electronic health records programmed to populate specific data fields in the electronic
281 case report form
- 282 • Randomization tools that assign subject numbers
- 283 • Barcode readers recording medications or devices
- 284 • Pharmacies
- 285 • Clinical study subjects (the data elements they provide might include patient reported
286 outcomes or informed consent).

287

288 Each study site should maintain on site a list of prospectively determined originators (persons,
289 devices, and instruments) of data elements authorized to transmit data elements to the eCRF.
290 The list of originators should be co-developed by the sponsor and the clinical investigator. The
291 list should include users' unique identifiers (e.g., user name) and the period for which
292 authorization for data entry was given (see Table 3 for examples). During an inspection, this list
293 will assist FDA's review of the audit trail for each data element. For devices and instruments,
294 the list should include any available unique device identifier, the manufacturer, the model
295 number, and the serial number. The list should be maintained to reflect staff changes that occur
296 during the conduct of the clinical study.

297

298

Table 3. – Example of List of Authorized Data Originators

Category of Data Originator	List of Authorized Data Originators	Authorization Time Period
Clinical staff	Dr John M Brown	January 2, 2008-December 4 2009
	Alice Smith RN	March 5, 2008-December 12, 2009
Automated laboratory output	American Clinical Laboratories	August 30 2008-January 5, 2009
	ClinPath Services	December 21, 2007-December 12, 2009

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Automated EKG machine output	Cardiology products, Model XG41, and Serial # 29834	May 13, 2008-December 12, 2009
	Cardiac monitors Inc, Model HG23, and Serial #45628	May 13, 2008-December 12, 2009
Electronic patient recorded outcome	Study subject VL0012	February 24, 2008-March 24, 2008
	Study subject VL0013	February 27, 2008- March 27, 2008
	Study subject VL0014	August 18, 2008-September 18, 2008

299

300

301

7. Identification of Data Originators

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304

305

For those who use electronic signatures based upon the use of identification codes in combination with passwords, the clinical site must employ controls to ensure the security and integrity of the authorized user names and passwords (21 CFR 11.300(a)). Controls should:

306

307

308

309

- Confirm that the password corresponds with the identity of the user
- Confirm that the user accepts responsibility for the validity of the data entered using that password

310

311

312

When electronic thumbprints or other biological identifiers are used in place of an electronic password, controls should:

313

314

315

316

- Confirm that the biological identifier corresponds with identity of the user
- Confirm that the user accepts responsibility for the validity of the data entered using that biological identifier

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320

321

When a device or instrument automatically populates a data field in the eCRF, a data element identifier should be created that identifies that particular device or instrument as the originator of the data element. For example, if an EKG machine automatically populates the eCRF, a data element identifying the manufacturer, model number, and serial number should be generated.

322

B. Tier 2 – Data Review

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325

1. The Investigator

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329

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331

332

Investigators are those individuals who actually conduct a clinical study (i.e., under whose immediate direction the investigational product is administered or dispensed to a subject). When a study is conducted by a team of individuals, the investigator is the responsible leader of the team (21 CFR 312.3(b) and 812.3(i)). Investigators are responsible for conducting the study according to the protocol and protecting the rights, safety, and welfare of study subjects (21 CFR 312.60 and 812.100). Investigators should evaluate and act on information emerging during the course of the study. To meet this responsibility, investigators should continually assess subject

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333 data to monitor clinical responses and to determine the need for treatment modifications.
334 Additionally, investigators must submit certain adverse events to the sponsor (see 21 CFR
335 312.64(b) and 812.150(a)(1) for additional information). The investigator must also record,
336 within each subject's case history, the observations related to the exposure of each subject to the
337 investigational product (21 CFR 312.62(b) and 812.140(a)(3)(iii)).
338

339 To comply with the requirement to maintain accurate case histories (21 CFR 312.62(b) and
340 812.140(a)(3)), investigators should review completed portions of the eCRF for each subject
341 before the data are archived and released to the parties in Tier 3 (see Fig. 1). The investigator
342 should indicate that he/she has reviewed the submitted data. For example, an investigator might
343 initiate an electronic command to enable transmission of data to parties in Tier 3, or append a
344 data element identifier (with the date, time, and originator's name), indicating that the
345 investigator has reviewed the data element. This command or appendage would be applied to all
346 the data elements belonging to the portion of an eCRF reviewed by the investigator.
347

348 All *sub-investigators* (i.e., any member of the study team other than the clinical investigator
349 responsible for the conduct of the study) who are involved in entering or signing off on data
350 elements in the eCRF should be assigned their own user names and passwords.
351

352 In exceptional circumstances, the protocol may require that certain data elements be hidden from
353 the investigator. Concurrence with this procedure should be obtained from FDA review
354 divisions. Such data elements may be forwarded directly to parties in Tier 3 without investigator
355 sign off.
356

2. The Investigator's Copy of the eCRF

358
359 The eCRF is the electronic document containing all data elements on a study subject that the
360 investigator has reviewed prior to release to parties in Tier 3 (e.g., the sponsors, CRO,
361 institutional review board). Portions of the eCRF may be released to parties in Tier 3 as the
362 study progresses. The procedure and timing for release before study completion by the
363 investigator should be included in the protocol. The eCRF should permanently carry the
364 electronic signature of the investigator who reviewed it.
365

366 The eCRF for each subject, along with the study design and study participation data, should be
367 stored as extensible markup language (XML) files following the current FDA Study Data
368 Exchange Standards.¹⁰
369

370 The physical location of data will vary, depending on the complexity and structure of the study.
371 For example, data reviewed and signed off by an investigator can be stored on a personal
372 computer, a network server, an internet server, and/or a variety of storage devices (e.g., DVDs,
373 removable drives). FDA recommends the following:
374

¹⁰ See <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.

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- 375 • The clinical investigator should generate a write-protected copy of the eCRF for the study
376 archives following review and sign off.
- 377 • The clinical investigator should maintain control of these copies.
- 378 • The clinical investigator must retain a file of these copies for a minimum length of time.
379 (See 21 CFR 312.62(c) and 812.140(d) for additional information.)
- 380 • The sponsor should describe in its standard operating procedures the location of the
381 copies so they are available to FDA inspectors as a reference for data validation.
- 382 • Archived copies of eCRFs and other electronic documents and records required by 21
383 CFR 312.62(b) and 812.140(a)(3) that are pertinent to the clinical study (e.g. laboratory
384 reports, pulmonary function test reports) should be available in read only format at the
385 site of the study. These may be requested by FDA during a site inspection (21 CFR
386 312.68 and 812.145).
- 387 • When an investigator has transcribed data elements from paper documents into an eCRF,
388 the investigator must also retain the paper documents for review by FDA (see 21 CFR
389 312.62(c) and 812.140(d)).
- 390 • During the clinical study, archived data elements should be available in read only format
391 to the originators who submitted them. For example, although the archived data may
392 reside in a personal computer, a Web-based repository, a central data server, or as a paper
393 archival copy, the laboratory should have access to the hemoglobin levels that it reports,
394 just as the study subject should be able to review data reported in a patient-reported
395 outcome tool or patient diary. The data that are part of the subject's case history may be
396 requested by FDA during a site inspection (21 CFR 312.68 and 812.145).
- 397 • The investigator's copy of the eCRF should be write-protected (read only) at the time of
398 investigator sign off. If necessary, amendments can be made separately with an
399 appropriate audit trail, including the originator, date and time of the amendment, and
400 reason for the amendment (see section III.A.3 of this document).

C. Tier 3 -- Data Processing and Transmission

402 Various available technologies can be used to acquire and transmit data electronically, provided
403 the security of the information can be ensured and access to the system containing the data is
404 limited to authorized password holders. Examples include traditional programs run from
405 personal computers, Web-based systems, hand-held devices, or automatic output from laboratory
406 instruments or medical devices.

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409 Electronic data acquisition enables real-time transmission of data during the progress of a
410 clinical study. For example, following investigator sign off, a sponsor may choose to
411 automatically transmit blinded laboratory data directly into a central *safety* archive, and these
412 data may be transmitted to a data and safety monitoring board. As part of a sponsor's designated
413 monitoring responsibilities, a sponsor may choose to transmit study data to a CRO for real-time
414 evaluation.
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417 Sponsors should describe which data elements will be transmitted electronically, the origin and
418 destination of the data elements, the parties with access to the transmitted data elements, when to
419 transfer, and any actions, such as protocol modification, that may be triggered by real-time
420 review of those data elements. Authorized changes to the electronic source data by the originator
421 should be transmitted to all the data destinations. Blinding should not be compromised during
422 the transmission of data prior to completion of the study.

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IV. REGULATORY REVIEW COLLABORATION

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427 In an effort to facilitate the review of submissions and ensure that FDA's requirements are
428 satisfied, FDA's review divisions are available to review with sponsors their plans for the
429 handling of electronic source data before implementation of a computerized system.

430
431 Detailed information on software development and the use of computerized systems in clinical
432 studies can be found in FDA's guidances on the *General Principles of Software Validation* and
433 *Computerized Systems Used in Clinical Investigations*.

434
435 Sponsors should include in their protocols information about the intended use of computerized
436 systems during the conduct of a clinical study. Protocols should include a description of the
437 security measures employed to protect the data in each case, and a detailed diagram and
438 description of the transmission of electronic data.

439
440 Sponsors should also include information in the protocol about electronic tools intended to be
441 used to detect events in the eCRF such as, but not limited to, data inconsistencies, missing data,
442 and entries out of range. Logs to record errors that are detected during the progress of a clinical
443 study should be included.

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GLOSSARY OF TERMS

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The following is a list of definitions of terms used in this guidance document.

Audit Trail: A process that captures details such as additions, deletions, or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the course of such details relating to the electronic record.

Certified Copy: A copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

Computerized System: 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 study.

Data Element: A single observation associated with a subject in a clinical study. Examples include birth date, white blood cell count, pain severity measure, and other clinical observations made and documented during a study.

Data Element Identifier: A write-protected information tag attached to a data element that includes the origin of the data element, the date and time of entry, and the identification number of the study subject to whom the data element applies.

Data Originator: A person, device, or instrument authorized to enter the data element into the eCRF.

Direct Entry: Initial recording of data into an electronic record. Examples are the keying by an individual of original observations into a system, or automatic recording by a system of the output of a balance that measures a 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 (21 CFR 11.3(b)(6)).

Electronic Signature: An *electronic signature* is 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 (21 CFR 11.3(b)(7)).

Read Only: Electronic material that can be viewed but cannot be altered or deleted.

Source Data: Also known as *original data*, those values that represent the first recording of clinical trial data elements.

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488 **Source Documents:** Original documents and records including, but not limited to, hospital
489 records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation
490 checklists, pharmacy dispensing records, recorded data from automated instruments, copies or
491 transcriptions certified after verification as being accurate and complete, microfiches,
492 photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at
493 the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical
494 trial. A case report form may serve as a source document if data elements are newly created and
495 not transcribed from other sources.

496
497 **Transmit:** To transfer data within or among clinical study sites, CROs, data management
498 centers, or sponsors.

499
500 **Write-Protected:** Information protected by a mechanism that prevents alteration or deletion of
501 data.