Use of Electronic Informed Consent in Clinical Investigations

Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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Center for Biologics Evaluation and Research (CBER)
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Procedural

Contains Nonbinding Recommendations

Draft — Not for Implementation

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Guidance for Industry

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TABLE OF CONTENTS

Use of Electronic Informed Consent in Clinical Investigations Questions and Answers Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This guidance provides recommendations for clinical investigators, sponsors, and institutional review boards (IRBs) on the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices, and combinations thereof. FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs are set forth in 21 CFR parts 11, 50, and 56, respectively.[2] The information presented to the subject,[3] processes used for obtaining informed consent, and documentation of the electronic informed consent (eIC) must meet the requirements of these and other applicable regulations.

For the purposes of this guidance, *electronic informed consent* refers to using electronic systems and processes that may employ multiple electronic media (e.g., text, graphics, audio, video, podcasts and interactive Web sites, biological recognition devices, and card readers) to convey information related to the study and to obtain and document informed consent.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and the Office of Good Clinical Practice (OGCP) in the Office of Medical Products and Tobacco in coordination with the Center for Biologics Evaluation Research (CBER) and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration. This guidance document was developed in consultation with the Department of Health and Human Services' Office of Human Research Protections.

[2] 21 CFR parts 50 and 56 apply to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products (§§ 50.1 and 56.101).

[3] In this guidance, we do not distinguish between subjects and potential or prospective study subjects. Please note that subjects are considered potential or prospective study subjects until the consent document is signed.

This guidance provides recommendations on procedures that may be followed when using an eIC to help:

- Ensure protection of the rights, safety, and welfare of human subjects
- Ensure the subject's comprehension of the information presented during the eIC process
- Ensure that appropriate documentation of consent is obtained when electronic media and processes are used to obtain informed consent[4]
- Ensure the quality and integrity of eIC data[5] included in FDA applications and made available to FDA during inspections

Although FDA believes that the informed consent process begins with subject recruitment,[6] recommendations on using electronic media and processes for subject recruitment are outside the scope of this guidance.

Other applicable recommendations may be found in the following guidance documents: [7]

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

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

To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services Office for Human Research Protections and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This guidance document was developed as a part of these efforts.

[4] Investigators are required to prepare and maintain records as described in §§ 312.62 and 812.140(a). Similarly, sponsors are required to maintain records relating to an investigation as described in §§ 312.57 and 812.140(b).

[5] For the purposes of this guidance, eIC data includes the template and site-specific versions of eIC, materials submitted to IRBs for review and approval, all amendments to the template and site-specific eICs, required informed consent elements presented to the subject during the eIC interview process, and the electronic signature of the subject, including the date when the subject or the subject's LAR signed the eIC.

[6] For more information on subject recruitment, see the guidance for institutional review boards and clinical investigators: *Recruiting Study Subjects - Information Sheet.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance Web page at www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] See also the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet.* When finalized, this guidance will represent FDA's current thinking on its informed consent regulations.

II. BACKGROUND

To many, the term *informed consent* is mistakenly viewed as synonymous with obtaining a hand-written signature from the subject or the subject's legally authorized representative (LAR)[8] on a written informed consent form. FDA believes that obtaining a subject's oral or written informed consent is only part of the consent process. Informed consent involves providing a potential subject with adequate information about the research to allow for an informed decision about the subject's voluntary participation in the clinical investigation. Informed consent must include a process that facilitates the subject's comprehension of the information and allows adequate opportunity for the subject to ask questions and consider whether or not to participate (§ 50.20). Furthermore, this process often continues beyond obtaining the subject's initial consent at the time of enrollment. It may involve providing information as the clinical investigation progresses or as the subject or situation requires. The elements of informed consent for human subjects and the requirements for documentation of informed consent are discussed in §§ 50.25 and 50.27, respectively.

The clinical research community is showing greater interest in using electronic media to provide information usually contained within the written informed consent document, evaluate the subject's comprehension of the information presented, and document the consent of the subject or the subject's LAR. Electronic processes to obtain informed consent may use an interactive interface for the informed consent process, which may facilitate the subject's ability to retain and comprehend the information.[9,10] Furthermore, these electronic processes may allow for rapid notification to the subjects of any amendments pertaining to the informed consent that may affect their willingness to continue to participate. Electronic processes may also promote timely entry of any eIC data into the study database and allow for timely collection of the subject's informed consent data from remote locations.

III. INSTITUTING AN ELECTRONIC INFORMED CONSENT

QUESTIONS AND ANSWERS

Q1. How should the information in the eIC be presented to the subject?

The eIC must contain all elements of informed consent required by FDA regulation (§ 50.25). The information presented must be in language understandable to the subject or the subject's LAR (§ 50.20). *Understandable* means that the information presented to subjects is in a language and at a reading level the subject can comprehend (including the explanation of scientific and medical terms). All abbreviations should be spelled out at the time of first use.

[8] Legally authorized representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (§ 50.3(l)).

[9] Sonne SC, Andrews JO, Gentilin SM, et al. Development and pilot testing of a video-assisted informed consent process. Contemp Clin Trials. 2013; 36:25-31 (http://dx.doi.org/10.1016/j.cct.2013.05.011).

[10] Rowbotham MC, Astin J, Greene K, Cummings SR. Interactive Informed Consent: Randomized Comparison with Paper Consents. PLoS One. 2013; 8(3): e58603. doi:10.1371/journal.pone.0058603.

If the eIC programs are interactive, they should be easy to navigate, allowing the user to proceed forward or backward within the system or stop and continue at a later time. Hyperlinks may be provided where helpful. Because some subjects may have difficulty navigating or using electronic systems because of, for example, lack of familiarity, poor eye sight, or impaired motor skills, steps should be taken to ensure that the eIC process is appropriate for these subjects. The eIC must be presented in a manner that minimizes the possibility of coercion or undue influence regarding the subject's decision to participate in a study (§ 50.20).

Q2. How and where may the eIC process be conducted?

FDA regulations require an investigator to obtain the informed consent of subjects (21 CFR part 50 and 21 CFR 312.60 and 812.100). If the investigator delegates this responsibility, the responsibility should be delegated to an individual qualified by education, training, and experience to perform this activity.[11]

The consent process may take place at the study site where both the investigator and subject are at the same location, or it may take place remotely (e.g., at the subject's home or another convenient venue) where the subject reviews the consent document in absence of the investigator. The eIC materials may be provided for both on-site and remote access.

If the entire process takes place at the study site, the study personnel can personally verify the subject's identification, review the eIC content, answer questions about the material, have follow-up discussions, and witness the signing of the eIC.

If any or all of the process takes place at a remote location, all interactive responses by subjects, witnesses, or other involved parties should be documented electronically using software systems to ensure that responses cannot be altered. In addition, if the consent process is not personally witnessed by study personnel, the computerized system should include a method to ensure that the person signing the informed consent is the subject who will be participating in the research study (or the subject's LAR). Whether the eIC is obtained from the subject on-site or remotely, the subject should have the opportunity to ask questions and receive answers prior to signing the eIC to participate in the study.

Q3. How and when should questions from subjects be answered?

The eIC interview process should allow subjects the opportunity to ask questions about the study. This may be accomplished by in-person discussions with study personnel or by using a combination of electronic messaging, telephone calls, videoconferencing, or a live chat with a remotely located clinical investigator or appropriately delegated study personnel. The electronic systems should ensure the security of the data as well as the subject's privacy when such electronic communication tools are used as part of the informed consent interview process. Subjects should also be given a description of how and when they will receive answers to their questions and must be provided information on how to contact an appropriate individual for

[11] See the guidance for industry *Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects.*

pertinent questions about the clinical investigation and the subjects' rights and whom to contact in the event that a research-related injury to the subject occurs (§ 50.25(a)(7)).

Q4. What steps may be taken to facilitate the subject's understanding of the information being presented?

The eIC computer program may contain various methods to help an investigator assess the subject's understanding of the information being presented during the eIC interview process. To aid the subject in understanding the material, the eIC may use interactive computer-based technology, which may include diagrams, images, graphics, video technology and narration, as appropriate.

If an interactive computer program is used, the program should be appropriate for the intended audience, taking into consideration the subject's age, language, and comprehension level. In addition, programs may be enhanced by including questions at the end of each section of the eIC interview process that help assess the subject's understanding and awareness of the informed consent materials. These and other tests may be used to verify comprehension of key study elements before the subject signs the informed consent to enter the study.

Q5. What steps may be taken to ensure that new or additional information is conveyed to the subject during the course of the clinical investigation?

When appropriate, the eIC process must ensure that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be transmitted to the subject or the subject's LAR (see § 50.25(b)(5)). In addition, if an update or amendment to an eIC is necessary and relates to the subject's willingness to continue participation in the study, the process should ensure that the subject is given an adequate opportunity to ask questions about the amended contents. The process should also ensure that the subject or the subject's LAR signs the amended eIC in a timely manner and the signed amended eIC is archived appropriately. See Q11 for IRB responsibilities.

Q6. Does FDA allow the use of electronic signatures to document eIC?

When written informed consent is required, the use of electronic (including digital) signatures is permitted, provided the electronic signature is in compliance with applicable FDA regulations.[12] In such cases, the electronic signature is considered by FDA to be trustworthy, reliable, and generally equivalent to handwritten signatures executed on paper (see 21 CFR part 11, subpart A (11.1)(a)). The procedure for eIC may include an electronic method to capture the signature of the subject or the subject's LAR (e.g., an encrypted digital signature, electronic signature pad, voice print, digital fingerprint). However, FDA does not mandate a specific method of electronic signature. IRBs should consider applicable issues such as how the electronic signature is created, if the signature can be shown to be legitimate, and if the consent or permission document can be produced in hard copy for review by the subject upon request.

[12] See 21 CFR part 11. For additional information, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures – Scope and Application.*

The electronic system must capture and record the date that the subject or subject's LAR provides consent (§ 50.27(a)). A copy of the informed consent must be provided to the person signing the form (§ 50.27(a)) (see Q8).

Q7. What special considerations should be given to the use of eIC for pediatric studies?

The eIC process can be used to obtain assent from pediatric subjects (when required) and parental permission from their parent(s) or guardian. The general requirements for informed consent, found in §§ 50.25, 50.27, and 50.55, apply to parental permission.

Absent a waiver of the assent requirement, the IRB must determine that there are adequate provisions for soliciting the assent of children when, in the IRB's judgment, the children are capable of providing assent.[13] In addition, the IRB must determine whether and how assent must be documented.[14] The language and presentation of information must be understandable to the child, and the documentation of assent should be handled in the same way as documentation of informed consent/parental permission.

Q8. Should subjects receive a copy of their eIC and have easy access to the materials and information presented to them in their eIC?

Yes. FDA regulations require that the person signing the informed consent be given a copy of the written consent form (§ 50.27(a)). Although FDA regulations do not require that the subject's copy include a signature, FDA recommends that a copy of the signed consent form that includes the date when the eIC was signed be provided to the subject.

Some form of the consent document must be made available to the subject (or to the subject's LAR or the parents or guardians of subjects who are children) in a format that can be retained. For eIC, the copy of the informed consent document could be in the form of printed paper or an e-copy that can be transmitted by email or other form of electronic media. The copy (e.g., printed paper document or email with an e-copy) should include a transcript of any audiovisual presentations provided during the eIC process.

Should an e-copy be offered, subjects should be informed of the risks of storing or viewing the consent document on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Unlike paper copies, which the subject may refuse to retain or may destroy, e-copies delivered directly to the subject's PED may not be able to be permanently removed.

[13] See 21 CFR 50.55(a).
[14] See 21 CFR 50.55(g).

Q9. What steps can be taken to help ensure confidentiality of the information once eIC is obtained?

The computerized system that supports the eIC must be secure with restricted access[15] and should include methods to ensure confidentiality regarding the subject's identity, study participation, and personal information after informed consent has been obtained. If the entity holding the subject's personal information is a covered entity under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law No. 104-191) or a business associate of a HIPAA covered entity, the requirements in the HIPAA Privacy, Security, and Breach Notification Rules apply (see 45 CFR parts 160 and 164). For example, the subject's information within a computerized system must be encrypted unless the entity documents why encryption is not reasonable and appropriate in their specific circumstances and implements an equivalent alternative measure, if reasonable and appropriate.

Q10. Can HIPAA authorizations for research, which are frequently combined with informed consent documents, be obtained electronically?[16]

Yes. HIPAA authorizations may be obtained electronically, provided that the signature of the subject (or the subject's personal representative) is a valid electronic signature under applicable laws and regulations.[17] The Electronic Signatures in Global and National Commerce Act (E-Sign Act) (Public Law 106-229) addresses what constitutes a valid electronic signature, and provides that a signature may not be denied legal effect because it is in electronic form.

The HIPAA privacy rule requires that when a covered entity seeks an authorization from a subject (or a subject's personal representative), the covered entity must provide the individual with a copy of the signed authorization; this requirement also applies where a HIPAA authorization is obtained electronically.

Q11. What are the IRB's responsibilities in the eIC process?

FDA regulations require that an IRB review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by the IRB regulations (§ 56.109(a)). A critical part of this responsibility is for the IRB to ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in clinical investigations (§§ 56.109(b) and 56.111(a)(4)). Therefore, the IRB must review and approve the eIC and any amendments to the eIC (§ 56.109(a)). FDA recommends that an investigator discuss plans for using eIC with the IRB prior to finalizing development of the eIC to ensure that the IRB agrees that this format may be used for obtaining informed consent. IRBs should also be aware of site security and information and data use policies at their respective institutions.

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[15] See the HIPAA Security Rule (available at http://www.hhs.gov/ocr/privacy/hipaa/understanding/srsummary.html) and see 45 CFR part 160 and subparts A and C of part 164.

[16] For more information, see the guidance for industry *IRB Review of Stand-Alone HIPAA Authorizations Under FDA Regulations.*

[17] See the Electronic Signatures in Global and National Commerce Act (E-Sign Act) (Public Law 106-229) and 21 CFR part 11.

Q12. What eIC documentation does FDA require for submission with applications?

The investigational new drug application (IND) regulations do not specifically require submission of informed consent documents to FDA as part of an IND application; however, CDER and CBER may request submission of the informed consent for review[18] under certain circumstances (e.g., when unusual known clinical toxicity is associated with the study drug or class of drugs; when the study population is particularly vulnerable; when the clinical investigation has significant potential for serious risk to human subjects; or for a postmarket safety clinical trial, required under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[19] to assess a serious risk).[20] Although all informed consent documents used in clinical investigations regulated by the FDA must be reviewed by an IRB, there are situations in which CDER and CBER review of an informed consent in addition to IRB review is particularly important to determine whether a clinical investigation may safely proceed under 21 CFR part 312.

Investigational device exemption (IDE) regulations, however, state that IDE applications must include copies of all forms and informational materials to be provided to subjects to obtain informed consent (§ 812.20(b)(11)). When FDA approval of an IDE application is required, a sponsor must not begin an investigation until the IDE application, including the informed consent materials, have been reviewed and approved by FDA (see 21 CFR 812.20(a) and (b)).

The sponsor should submit to FDA the same eIC materials that will be presented to subjects to obtain eIC for their participation in the clinical investigation. For example, as part of an electronic submission to FDA, copies of all forms and informational materials should include any videos and Web-based presentations provided on a compact disk (CD) or as a link to the eIC Web page that is accessible to FDA for viewing these eIC materials. In addition, the sponsor should also provide a copy of the informed consent document as a paper copy or an electronic PDF format document that can be emailed that includes a transcript of the eIC audiovisual presentation.

Q13. What steps can be taken to ensure the system archives the documents appropriately?

FDA does not have a preferred method for archiving documents; however, the eIC process should incorporate procedures to ensure that electronic documents can be archived appropriately and all versions of the eIC can be retrieved easily. The system should have audit trail capability to capture any revisions to the eIC, the identity of the person making the changes, the reason for

[18] See 21 CFR 312.23(a)(11).

[19] 21 U.S.C 355(o).

[20] For additional information, see the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet.* When finalized, this guidance will represent FDA's current thinking on its informed consent regulations.

the changes, and the date the changes were made. All procedures must be in compliance with applicable FDA regulations for electronic records.[21]

If eIC data are stored on a remote computer, in a data storage center, or in "the cloud,"[22] (i.e., at multiple, dispersed sites), data privacy laws and regulations that apply to the remote storage site(s), in addition to those that apply to the research site, may apply and should be considered. Agreements with data storage and processing entities should acknowledge the investigators' and any business associates' responsibilities to comply with relevant requirements, and subjects should be informed of such arrangements as appropriate.

Q14. What materials or documents will FDA require during an inspection?

During inspections of clinical study sites,[23] FDA requires access to records and reports made by the investigator, including site-specific versions of eIC, materials submitted to IRBs for review and approval, all amendments to the site-specific eICs, and all subject-specific signed eICs.[24] These should be available at the site either in electronic or paper form. FDA reserves the right to review the content of the informed consent program or document and the corresponding consent of the subject, the subject's LAR, and a witness, where applicable, along with the date that the eIC was signed. Any updates to the documentation should also be available for review.

[21] For additional information regarding the use of electronic signatures, please refer to FDA regulations and guidance. See 21 CFR part 11, Electronic Records; Electronic Signatures and the guidance for industry *Part 11, Electronic Records; Electronic Signatures — Scope and Application*.

[22] "Cloud" computing is a model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g., networks, servers, storage, applications, and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction. For more information, see National Institute of Standards and Technology, U.S. Department of Commerce, *The NIST Definition of Cloud Computing*, available at http://www.nist.gov/itl/cloud/.

[23] See the information sheet guidance for IRBs, clinical investigators, and sponsors *FDA Inspections of Clinical Investigators* (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) and the FDA Compliance Program Guidance Manual (CPGM) 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008).

[24] Under the FD&C Act, FDA may inspect and copy all records relating to a clinical investigation (21 U.S.C. 374(a)(1)). See also 21 CFR 312.58, 312.68, and 812.145(b).