

## **Tip Sheet 11: Following the Guideline of the International Conference on Harmonisation – Good Clinical Practice (E6)**

**Related Accreditation Elements: I.1.D., I.1.F., I.7.B., II.2.G., II.3.F., II-4, II.4.C., III.1.C., III.1.E., III.1.F., III-2, III.2.B., and III.2.D.**

**Related Accreditation Table: II.3.F.1.**

ICH-GCP is an ethical and scientific quality guidance document that is used internationally in the conduct of clinical trials. It includes areas for designing, conducting, recording, and reporting research that involves the participation of human participants. The guidance has its origins in the Declaration of Helsinki and was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO)<sup>1</sup>. ICH-GCP provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate mutual acceptance of data from clinical trials by regulatory authorities in these jurisdictions. ICH-GCP contains guidelines for quality, safety, efficacy, and additional multidisciplinary guidelines. AAHRPP Standards include requirements under ICH-GCP (E6). The current version of the ICH-GCP guideline is (R2) but is referred to as the ICH-GCP (E6) guideline in this Tip Sheet.

In addition to general recommendations when following the ICH-GCP (E6) guideline, this Tip Sheet contains an Appendix that groups all the requirements consistent with AAHRPP's Domains. The Tip Sheet has sections for the organization (Domain I), Institutional Review Board (IRB) or Ethics Committee (EC) (Domain II), and researcher (Domain III). All of these sections have requirements that are unique to this guideline and above those required in AAHRPP's Essential Requirements. AAHRPP has identified those unique ICH-GCP (E6) requirements and has included them in its Standards outlined in the [Evaluation Instrument for Accreditation](#) for those organizations that follow ICH-GCP (E6).

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<sup>1</sup> For organizations outside the US, please consult the appropriate AAHRPP addendum for that country.

## Helpful Hints:

### Domain I: The Organization

#### *Scope*

An organization should determine ICH-GCP (E6)'s applicability. That is,

1. Is ICH-GCP (E6) applied to all research conducted by the organization or limited to certain types of research (e.g., industry-sponsored clinical trials)? (Element I.1.A.)
2. Are all requirements of ICH-GCP (E6) followed or limited to certain areas (e.g. IRB/IEC section only)? (Element I.1.A.)
3. If the sponsor requires ICH-GCP (E6) be followed, the organization should inform the sponsor if the organization does not follow all of ICH-GCP (E6).
4. If there is a contract or funding agreement that requires ICH-GCP (E6) be followed, the contract should include the extent or limit that the organization follows ICH-GCP (E6). (Standard I-8)

#### *Administration*

1. Organizations that do not apply ICH-GCP (E6) to all research may want to create a separate policy, reviewer form, or other materials specifically focused on ICH-GCP (E6). (Element I.1.A.)
2. Organizations should ensure researchers and research staff, IRB or EC members, and contracts and grants staff are knowledgeable about requirements of ICH-GCP (E6). (Element I.1.E.)
3. Organizations may want to create researcher and research staff manuals or educational materials that explain the additional requirements when following ICH-GCP (E6). (Element I.1.E.)
4. Organizations should create workflows so that grants and contracts staff can communicate to the IRB or EC when sponsors require compliance with ICH-GCP (E6) so that the IRB or EC considers this when conducting its review. (Standard I-8)

### Domain II: The Institutional Review Board

#### *Scope*

1. Indicate how IRB or EC chairs, vice-chairs, members, staff, and researchers and research staff are educated about ICH-GCP (E6) requirements and to which research ICH-GCP (E6) is applied. (Element II.1.A.)

#### *Administration*

1. Organizations may want to add documentation that the IRB or EC reviewed the study in compliance with ICH-GCP (E6), such as in the IRB or EC approval letter or in an electronic system so that monitors can confirm the IRB or EC considered this in its review. (Element II.5.B.)

### Domain III: Researchers and Research Staff

If the sponsor does not provide source documents, the study team may want to create study-specific source documents to assist with protocol compliance. (Element III.2.C)

### Appendix: References to ICH-GCP in Evaluation Instrument

1. Written materials include a statement that clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements. (AAHRPP I.1.D.(4)(a) (page 28); ICH-GCP 2.1)
2. Written materials include the evaluation of the available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial. (AAHRPP I.1.F.(4)(a) (page 35); ICH-GCP 2.4)
3. The scientific review process evaluates:
  - a. The soundness of the research design (AAHRPP Element I.1.F.(4)(c)(i) (page 35); ICH-GCP 2.5)
  - b. The ability of the research to answer the proposed questions. (AAHRPP Element I.1.F.(4)(c)(ii) (page 35); ICH-GCP 2.5)
4. Where allowed or required, the researcher or organization may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the researcher or organization. (AAHRPP Element I.7.B.(2)(a)(ii) (page 73); ICH-GCP 4.6.2)
5. The researcher, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants. The researcher maintains records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor. (AAHRPP I.7.B.(2)(a)(iii-iv) (page 73); ICH-GCP 4.6.3)
6. Written materials define the problems researchers have to report to the IRB or EC to include:
  - a. New information that may affect adversely the safety of the participants or the conduct of the clinical trial. (AAHRPP II.2.G(6)(a)(i) (page 152); ICH-GCP 3.3.8(b))
  - b. Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants. (AAHRPP II.2.G(6)(a)(ii) (page 152); ICH-GCP 3.3.8(d))

7. Written materials on documentation of the consent process include:
  - a. Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the participant or by the participant's legally acceptable representative. (AAHRPP II.3.F.(8)(b)(i) (page 183); ICH-GCP 4.8.8)
  - b. Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion. (AAHRPP II.3.F.(8)(b)(i) (page 183); ICH-GCP 4.8.8)
  - c. If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. (AAHRPP II.3.F.(6)(b)(iii) (page 183); ICH-GCP 4.8.9)
    - i. After the written consent document and any other written information to be provided to participants is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document. (AAHRPP II.3.F.(6)(a)(iii)(A) (page 183); ICH-GCP 4.8.9)
    - ii. By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that consent was freely given by the participant or the participant's legally acceptable representative. (AAHRPP II.3.F.(6)(b)(iii)(B) (page 184); ICH-GCP 4.8.9)
    - iii. Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants. (AAHRPP II.3.F.(6)(b)(iii)(C) (page 184); ICH-GCP 4.8.11)
8. The consent disclosure includes the following additional disclosures:
  - a. The approval or favorable opinion by the IRB or EC. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.1.)
  - b. The probability for random assignment to each treatment. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (c))
  - c. The participant's responsibilities. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (e))
  - d. When applicable, the reasonably foreseeable risks or inconveniences to an embryo, fetus, or nursing infant. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (g))

- e. The important potential benefits and risks of the alternative procedures or courses of treatment that may be available to the participant. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (i))
  - f. When there is no intended clinical benefit to the participant, the participant should be made aware of this. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (h))
  - g. That the monitors, the auditors, the IRB or EC, and the regulatory authorities will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access. (AAHRPP Table II.3.F.1. (page 188); ICH-GCP 4.8.10 (n))
9. When adults are unable to consent, written materials have the IRB or EC determine:
- a. A non-therapeutic clinical trial (i.e., a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document. (AAHRPP Element II.4.A. (8)(a)(i) (page 202); ICH-GCP 4.8.13)
  - b. Non-therapeutic clinical trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
    - i. The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally. (AAHRPP Element II.4.A. (8)(a)(ii)(A); ICH-GCP 4.8.14)
    - ii. The foreseeable risks to the participants are low. (AAHRPP Element II.4.A. (8)(a)(ii)(B) (page 202); ICH-GCP 4.8.14)
    - iii. The negative impact on the participant's wellbeing is minimized and low. (AAHRPP Element II.4.A. (8)(a)(ii)(C) (page 202); ICH-GCP 4.8.14)
    - iv. The clinical trial is not prohibited by law. (AAHRPP Element II.4.A.(8)(a)(ii)(D) (page 202); ICH-GCP 4.8.14)
    - v. The opinion of the IRB or EC is expressly sought on the inclusion of such participants, and the written opinion covers this aspect. (AAHRPP Element II.4.A. (8)(a)(ii)(E) (page 202); ICH-GCP 4.8.14) Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed. (AAHRPP Element II.4.A.(8)(a)(ii)(E) (page 202); ICH-GCP 4.8.14)
10. Written materials require that the participant or the participant's legally authorized representative is informed about the clinical trial as soon as possible and provides consent

if the participant wishes to continue. (AAHRPP Element II.4.C.(4)(a) (page 211); ICH-GCP 4.8.15)

11. A qualified physician (or dentist, when appropriate), who is a researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions. (AAHRPP Element III.1.C.(2)(d) (page 239); ICH-GCP 4.3.1)
12. During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial. (AAHRPP Element III.1.C. (3)(a)(i) (page 227) and III.2.A.(2)(e) (page 239); ICH-GCP 4.3.2)
13. Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware. (AAHRPP Element III.1.C.(3)(a)(i) (page 227); ICH-GCP 4.3.2)
14. The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the sponsor any premature unblinding. (AAHRPP Element III.1.C.(3)(a)(ii) (page 227); ICH-GCP 4.7)
15. The researcher informs the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed. (AAHRPP Element III.1.E.(8)(a)(i) (page 232); ICH-GCP 4.3.3)
16. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the researcher makes a reasonable effort to ascertain the reason, while fully respecting the participant's rights. (AAHRPP Element III.1.E.(8)(a)(ii) (page 232); ICH-GCP 4.3.4)
17. Written materials describe that researchers and research staff provide all the disclosures and follow the requirements pertaining to consent covered by ICH-GCP. (AAHRPP Element III.1.F.(7)(a) (page 234); ICH-GCP 4.8)
18. The researcher provides evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB or EC, or the regulatory authority. (AAHRPP Element III.2.A.(b) (page 239); ICH-GCP 4.1.1)
19. The researcher is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the Sponsor. (AAHRPP Element III.2.A.(2)(c) (page 239); ICH-GCP 4.1.2)
20. The researcher ensures the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor. (AAHRPP Element III.2.A.(2)(f) (page 239); ICH-GCP 4.9.1)

21. The researcher must maintain a list of appropriately qualified persons to whom they have delegated significant clinical trial-related duties. (AAHRPP Element III.2.B.(3)(a) (page 242); ICH-GCP 4.1.5)
22. The researcher reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. The researcher follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB or EC. (AAHRPP III.2.D.(10)(a)(i) (page 249); ICH-GCP 4.11.1)
23. The researcher reports adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol. (AAHRPP Element III.2.D.(10)(a)(ii) (page 249); ICH-GCP 4.11.2)
24. For reported deaths, the researcher supplies the sponsor and the IRB or EC with any additional requested information (e.g., autopsy reports and terminal medical reports). (AAHRPP III.2.D.(10)(a)(iii) (pages 249-250); ICH-GCP 4.11.3)
25. The researcher provides written reports to the sponsor, the IRB or EC, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants. (AAHRPP III.2.D.(10)(a)(iv) (page 250); ICH-GCP 4.10.2)
26. If the researcher terminates or suspends a clinical trial without prior agreement of the sponsor, the researcher informs the organization, sponsor, and the IRB or EC. (AAHRPP III.2.D.(10)(a)(v) (page 250); ICH-GCP 4.12.1)
27. If the IRB or EC terminates or suspends approval of the clinical trial, the researcher promptly notifies the sponsor. (AAHRPP III.2.D.(10)(a)(vi) (page 250); ICH-GCP 4.12.3)
28. Upon completion of the clinical trial, the researcher informs the organization; the IRB or EC with a summary of the trial's outcome; and the regulatory authority with any reports required. (AAHRPP III.2.D.(10)(a)(vii) (page 250); ICH-GCP 4.13)