



Guidance: International Conference on Harmonization Good Clinical Practice (ICH-GCP)

1. Introduction

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical research that involves human participants in research. A sponsor may require that the FDA-approved protocol and any investigator SOPs associated with that protocol would assure ICH-GCP compliance in addition to any other regulatory or institutional requirements that apply to the research study.

2. Compliance Review of Research Following ICH-GCP E6(R2)

When U-M agrees to a research contract indicating a study will be conducted in full compliance with ICH-GCP, the sponsor, oversight agencies such as FDA, and U-M will apply ICH-GCP requirements in their compliance review of that study.

3. IRB Review of Research Following ICH-GCP E6(R2)

When reviewing research following ICH-GCP, the IRB will make the determinations required by the institutional policy and will also review the research plan submitted to identify aspects that may be inconsistent with ICH-GCP. Such review will include evaluation of the adequacy of the available nonclinical and clinical information on an investigational product to support the proposed clinical research study, and a review that proposed clinical research is scientifically sound and answers the proposed questions.

4. Investigator Responsibilities

Investigators should be fully aware of their obligations and responsibilities required by the institutional policy and applicable regulatory agencies prior to conducting research. This section provides a summary of investigator responsibilities pertinent to data and document management in accordance with the ICH-GCP (E6) Guideline. Investigators who agree to perform research represented to be ICH-GCP-compliant are required to follow the protocol as written and will be advised by the IRB to review all investigator obligations in the ICH-GCP as well as any aspects of ICH-GCP incompletely or not at all captured in the research protocol and investigator SOPs. To that end, investigators should reference the [full ICH-GCP \(E6\) Guideline](#). For additional training on Good Clinical Practice, see [HRPP Education Resources](#)

4.1 Investigator Qualification and Agreements (E6(R2) 4.1)

The investigator is qualified by education, training, and experience to assume responsibility for the proper conduct of the research; the investigator meets all the qualifications specified by the applicable regulatory requirement(s), and will provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authority(ies). (4.1.1)

The investigator is thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor. (4.1.2)

The investigator is aware of the [ICH-GCP \(E6\) Guideline](#) and the applicable regulatory requirements. (4.1.3)

The investigator must permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities. (4.1.4)

The investigator must maintain a list of appropriately qualified persons to whom significant research-related duties have been delegated.(4.1.5)

4.2 Adequate Resources (E6(R2) 4.2)

The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period. (4.2.1)

The investigator should have sufficient time to properly conduct and complete the research within the agreed period. (4.2.2)

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the research study to conduct the research properly and safely. (4.2.3)

The investigator should ensure that all persons assisting with the research are adequately informed about the protocol, the investigational product(s), and their research-related duties and functions. (4.2.4)

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. (4.2.5)

If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. (4.2.6)

4.3 Medical Care of Research Participants (E6(R2) 4.3)

A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the research study, should be responsible for all research-related medical (or dental) decisions. (4.3.1)

During and following a participant's participation in a research study, the investigator should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the research. The investigator should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. (4.3.2)

It is recommended that the investigator inform the participant's primary physician about the participant's participation in the research study if the participant has a primary physician and if the participant agrees to the primary physician being informed. (4.3.3)

Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a research study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. (4.3.4)

4.4 Communication with the IRB (E6(R2) 4.4)

Before initiating a research study, the investigator should have written and dated approval/favorable opinion from the IRB for the research protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements), and any other written information to be provided to participants. (4.4.1)

As part of the investigator's written application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the research, the investigator should supply a copy of the updated Investigator's Brochure to the IRB. (4.4.2)

During the research the investigator should provide to the IRB all documents subject to review. (4.4.3)

During the research, the investigator will report to the IRB the following:

- New information that may affect adversely the safety of the participants or the conduct of the research study.
- Any changes significantly affecting the conduct of the research study or increasing the risk to participants. (3.3.8)

4.5 Compliance with the IRB-Approved Research Application (E6(R2) 4.5)

The investigator should conduct the research in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB. The investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement. (4.5.1)

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to research participants, or when the change(s) involves only logistical or administrative aspects of the research (e.g., change in monitor(s), change of telephone number(s)). (4.5.2)

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. (4.5.3)

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to research participants without prior IRB approval, and submit a modification to explain the deviation to the IRB as soon as possible. (4.5.4)

4.6 Investigational Product(s) (E6(R2) 4.6)

Responsibility for investigational product(s) accountability at the research site(s) rests with the investigator (or an appropriately qualified designee). (4.6.1)

The investigator should assign some or all of the investigator's duties for investigational product(s) accountability at the research site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator. (4.6.2)

The investigator should maintain records of the product's delivery to the research site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and research participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. (4.6.3)

The investigator should ensure that the investigational product(s) are stored as specified by the sponsor and in accordance with applicable regulatory requirement(s). (4.6.4)

The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol. (4.6.5)

The investigator, or a person designated by the investigator, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the research, that each participant is following the instructions properly. (4.6.6)

4.7 Randomization Procedures and Unblinding (E6(R2) 4.7)

The investigator should follow the research study's randomization procedures, if any, and should ensure that the code is broken only in accordance with the IRB-approved research application. If the research is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Research Participants (E6(R2) 4.8)

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the research study, the investigator should have the IRB's written approval/favorable opinion of the written informed consent form and any other written information to be provided to participants. (4.8.1)

The investigator should ensure that the written informed consent form and any other written information to be provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised consent form and other written information provided to participants must receive the IRB's approval in advance of use. The participant or the participant's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the research, and the communication of this information should be documented. (4.8.2)

The investigator should ensure that neither the investigator nor the research staff will coerce or unduly influence a participant to participate or to continue to participate in the research. (4.8.3)

The investigator should ensure that none of the oral and written information concerning the research, including the written informed consent form, contains any language that causes the participant or the participant's legally authorized representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence. (4.8.4)

The investigator, or a person designated by the investigator, should fully inform the participant or, if the participant is unable to provide informed consent, the participant's legally authorized representative, of all pertinent aspects of the research including the written information and the approval by the IRB. (4.8.5)

The investigator should ensure that the language used in the oral and written information about the research, including the consent form, will be as non-technical as practical and will be understandable to the participant or the participant's legally authorized representative and the impartial witness, where applicable. (4.8.6)

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the participant or the participant's legally authorized representative ample time and opportunity to inquire about details of the research and to decide whether or not to participate in the research study. All questions about the research should be answered to the satisfaction of the participant or the participant's legally authorized representative. (4.8.7)

Prior to a participant's participation in the research study, the investigator should ensure that the written informed consent form is signed and personally dated by the participant or by the participant's legally authorized representative, and by the person who conducted the informed consent discussion. (4.8.8)

If a participant is unable to read or if a legally authorized representative is unable to read, the investigator should ensure that an impartial witness is present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants, is read and explained to the participant or the participant's legally authorized representative, and after the participant or the participant's legally authorized representative has orally consented to the participant's participation in the research and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally authorized representative, and that informed consent was freely given by the participant or the participant's legally authorized representative. (4.8.9)

The investigator will ensure that both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:

- That the study involves research.
- The purpose of the research.
- The research study treatment(s) and the probability for random assignment to each treatment.
- The research study procedures to be followed, including all invasive procedures.

- The participant's responsibilities.
- Those aspects of the research that are experimental.
- The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
- The compensation and/or treatment available to the participant in the event of research-related injury.
- The anticipated prorated payment, if any, to the participant for participating in the research.
- The anticipated expenses, if any, to the participant for participating in the research.
- That the participant's participation in the research study is voluntary and that the participant may refuse to participate or withdraw from the research, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of research study procedures and/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 informed consent form, the participant or the participant's legally authorized representative is authorizing such access.
- That records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the participant's identity will remain confidential.
- That the participant or the participant's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the research.
- The person(s) to contact for further information regarding the research and the rights of research participants, and whom to contact in the event of research-related injury.
- The foreseeable circumstances and/or reasons under which the participant's participation in the research may be terminated.
- The expected duration of the participant's participation in the research.
- The approximate number of participants involved in the research. (4.8.10)

The investigator should ensure that, prior to participation in the research, the participant or the participant's legally authorized representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participants. During a participant's participation in the research, the participant or the participant's legally authorized representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants. (4.8.11)

The investigator should ensure that when a research study (therapeutic or non-therapeutic) includes participants who can only be enrolled in the research with the consent of the participant's legally authorized representative (e.g., minors, or patients with severe dementia), the participant should be informed about the research to the

extent compatible with the participant's understanding and, if capable, the participant should sign and personally date the written informed consent. (4.8.12)

The investigator should ensure that, except as described below, a non-therapeutic research study (i.e. a study 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 informed consent form. (4.8.13)

Non-therapeutic research studies may be conducted in participants with consent of a legally authorized representative provided the investigator ensures that the following conditions are fulfilled:

- The objectives of the research cannot be met by means of a research study with participants who can give informed consent personally.
- The foreseeable risks to the participants are low.
- The negative impact on the participant's well-being is minimized and low.
- The research is not prohibited by law.
- The approval/favorable opinion of the IRB is expressly sought on the inclusion of such participants, and the written approval/ favorable opinion covers this aspect.

Such research studies, 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 research studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed. (4.8.14)

The investigator should ensure that, in emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally authorized representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally authorized representative is not available, enrollment of the participant should require measures described in the protocol and/or elsewhere, with documented approval by the IRB, to protect the rights, safety and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally authorized representative should be informed about the research as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested. (4.8.15)

4.9 Records and Reports (E6(R2) 4.9)

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). (4.9.0)

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. (4.9.1)

The investigator should ensure that data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. (4.9.2)

The investigator should ensure that any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n) in the ICH-GCP E6 Guideline). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections. (4.9.3)

The investigator should maintain the research study documents as specified in [ICH-GCP \(E6\) Section 8: Essential Documents for the Conduct of a Clinical Trial](#) and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents. (4.9.4)

The investigator should ensure that essential documents are retained until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained. (4.9.5)

The investigator should ensure that the financial aspects of the study are documented in an agreement between the investigator and the sponsor. (4.9.6)

The investigator should make available for direct access all requested research-related records upon request of the monitor, auditor, IRB, or regulatory authority. (4.9.7)

4.10 Progress Report (E6(R2) 4.10)

The investigator will submit written summaries of the research status to the IRB annually, or more frequently if requested by the IRB. (4.10.1)

The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the research, and/or increasing risks to participants. (4.10.2)

4.11 Safety Reporting (E6(R2) 4.11)

The investigator should immediately report 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 immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the research participants rather than by the participants' names, personal identification numbers, and/or addresses. The investigator will also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the IRB and regulatory authority(ies). (4.11.1)

The investigator should report adverse events and/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. (4.11.2)

The investigator should supply the sponsor and the IRB with any additional requested information for reported deaths (e.g., autopsy reports and terminal medical reports). (4.11.3)

4.12 Premature Termination or Suspension of a Research Study (E6(R2) 4.12)

If the research study is prematurely terminated or suspended for any reason, the investigator should promptly inform the research participants, assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirement(s), inform the regulatory authority(ies). (4.12)

If the investigator terminates or suspends a research study without prior agreement of the sponsor, the investigator should inform the sponsor and the IRB. The investigator should provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. (4.12.1)

If the sponsor terminates or suspends a research study, the investigator should promptly inform the IRB and provide a detailed written explanation of the termination or suspension. (4.12.2)

If the IRB terminates or suspends its approval of a research study, the investigator should notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension. (4.12.3)

4.13 Final Report(s) by Investigator (E6(R2) 4.13)

Upon completion of the research study, the investigator should inform the IRB and provide the IRB with a summary of the research results, and provide any reports required by the regulatory authority(ies). (4.13)

5. Sponsor-Investigator Responsibilities

Investigators at U-M who initiate and submit IND or IDE applications to the FDA assume the responsibilities of both the investigator and the sponsor. See [OM Part 8.VII](#) for further guidance on the Sponsor-Investigator role and regulatory requirements.

Along with following any applicable regulatory requirements and U-M policies, sponsor-investigators who are complying with [ICH-GCP \(E6\) Guideline](#) should be familiar with applicable good manufacturing practice for manufacturing, handling, and storage of investigational articles. This section provides a summary of sponsor-investigator responsibilities pertinent to manufacturing, handling, and storage of investigational articles in accordance with the ICH-GCP (E6) Guideline.

5.1 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s) (E6(R2) 5.13)

The sponsor-investigator should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if

applicable. In addition, the labelling should comply with applicable regulatory requirement(s). (5.13.1)

The sponsor-investigator should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor-investigator should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations. (5.13.2)

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage. (5.13.3)

In blinded research studies, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding. (5.13.4)

5.2 Supplying and Handling Investigational Product(s) (E6(R2) 5.14)

The sponsor-investigator should ensure that written procedures include instructions that the investigator should follow for the handling and storage of investigational product(s) for the research study and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)). (5.14.3)

The sponsor-investigator should:

- Ensure timely delivery of investigational product(s).
- Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see [ICH-GCP \(E6\) Section 8: Essential Documents for the Conduct of a Clinical Trial](#)).
- Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after research completion, expired product reclaim).
- Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition. (5.14.4)

The sponsor-investigator should:

- Take steps to ensure that the investigational product(s) are stable over the period of use.
- Maintain sufficient quantities of the investigational product(s) used in the research to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the research data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period. (5.14.5)