IRB Policy 630 Requirements for the Application of Good Clinical Practice (GCP) to the Conduct of Clinical Trials

Scope

This policy describes the requirements, in addition to the Department of Health and Human Services (DHHS) – Office of Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations and Yale University Human Research Protection Program (HRPP) polices and procedures, for clinical trials involving human subjects to be compliant with Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (ICH-GCP Guidance (E6)).

Note: In the United States, the FDA has adopted GCP as guidance and not a regulatory requirement.

Policy Statement

The Yale University Institutional Review Boards (IRBs) comply with ICH GCP guidance (E6) only to the extent that it is compatible with FDA and DHHS regulations.

However, for industry-sponsored studies with contract requirements for institutional adherence to ICH GCP guidance (E6), the Yale University IRBs will comply with all of the GCP statements outlined in the ICH-GCP (E6) guidance, provided that:

a) The Principal Investigator (PI) indicates in the Human Investigation Committee (HIC) application(s) that the sponsor requires the IRB review process to comply with ICH standards, and

b) The Grants and Contracts Administration (GCA) Office confirms it is a contractual requirement

Note: Studies involving only behavioral interventions are not covered by this policy.

Reason for the Policy

Good Clinical Practice (GCP) guidance is an international “ethical and scientific quality standard” for designing, conducting, recording, and reporting clinical trials in human subjects that was developed by the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). The GCP guidance developed by ICH is based on FDA regulations for the protection of human subjects and defines the roles and responsibilities of Institutional Review Boards (IRBs), investigators, monitors, and sponsors.

General principles of ICH & GCP include, but are not limited to:

1. 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 requirement(s) (ICH-GCP 2.1)

2. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. (ICH-GCP 2.4)

3. Clinical trials should be scientifically sound, and described in a clear, detailed protocol. (ICH-GCP 2.5)

4. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol. (ICH-GCP 2.12)
Definitions

Clinical Trial/Study
Any investigation in human subjects intended to: discover or verify clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product; identify any adverse reactions to an investigational product; and/or study absorption, distribution, metabolism, and excretion of an investigational product to determine its safety and/or efficacy. The terms clinical trial and clinical study are synonymous. (ICH-GCP 1.12)

Good Clinical Practice (GCP): Also referred to as ICH E6.
A standard established by the International Conference on Harmonization for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of clinical trial subjects are protected. (ICH-GCP 1.24)

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).
Voluntary, international initiative to increase coordination of the requirements for developing and marketing new drugs. The ICH includes representatives from the pharmaceutical industry and regulatory authorities from the United States, Japan and the European Union.

Investigational Product
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. (ICH-GCP 1.33)

Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (ICH-GCP 1.34)

Legally Acceptable Representative
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 clinical trial. (ICH-GCP 1.37)

Note: Legally Acceptable Representative is only used in this context for clinical trials that follow ICH-GCP (E6) as listed in the policy statement.

Sponsor-Investigator
An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than the individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (ICH-GCP 1.54)

Policy Sections

630.1 Institutional Review Board (IRB) Responsibilities
Yale University voluntarily apply the ICH-GCP (E6) Guidelines to certain types of human subjects research conducted under its Human Research Protection Program. In general, Yale University apply ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations. When a sponsor requires institutional ICH-GCP compliance, the IRB will conduct a review in accord with ICH-GCP requirements.

To be approved, clinical trials must satisfy the requirements described in the Human Research Protection Program (HRPP) policies and procedures (see IRB Policy 100 – IRB Review of Research Protocols Involving Human Participants).

Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for the use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, Investigator’s Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB may require to fulfill its responsibilities. (ICH-GCP 3.1.2)
Yale University HRPP/IRB Practice Differences: The investigator’s current curriculum vitae (CV) is not requested at the time of submission of the protocol to the IRB. The qualifications of the investigator are confirmed and approved by the investigator’s Department Chair prior to submission to the Human Investigation Committee (HIC). The IRB verifies that the investigator has completed all requisite training and is in compliance with conflict of interest training and financial disclosure policies. In addition, the investigator is required to report on the IRB application whether or not their hospital privileges allow them to perform the specific procedures outlined in the protocol and directs them to the Hospital Department of Physician Services, should credentialing be required.

630.2 Informed Consent Requirements
In addition to the required elements of consent disclosure described by HRPP Policy 200: Informed Consent for Research Involving Human Participants and the ICH-GCP 4.8 – Informed Consent of Trial Subjects informed consent disclosures will include the following:

- That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject’s original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject’s legally acceptable representative is authorizing such access. (ICH-GCP 4.8.10(n))

- Prior to the beginning of the trial, the investigator should have the IRB written approval of the written informed consent form and any other written information to be provided to the subjects. (ICH-GCP 4.8.1)

Documentation of the informed consent of clinical trial subjects process include:

- Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subjects legally acceptable representative (LAR), and by the person who conducted the informed consent discussion. (ICH-GCP 4.8.8)

- If a subject 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. After the written informed consent and any other written information to be provided to subjects, is read and explained to the subject or subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial 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 subject or subject’s legally acceptable representative, and that informed consent was freely given by the subject or subject’s legally acceptable representative. (ICH-GCP 4.8.9)

- Prior to participation in the trial, the subject or the subject’s legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. (ICH-GCP 4.8.11)

630.3 Vulnerable Populations
Except as described below (ICH-GCP 4.8.14), a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject should be conducted in subjects who personally give consent and who sign and date the written informed consent form (ICH-GCP 4.8.13)

Non-therapeutic clinical trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- The objectives of the clinical trial cannot be met by means of a trial in subjects who can give consent personally
- The foreseeable risks to the subjects are low
- The negative impact on the subject’s well being is minimized and low
- The clinical trial is not prohibited by law
Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed. (ICH-GCP 4.8.14)

630.4 Investigator(s) Qualifications

1. The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should 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). (ICH-GCP 4.1.1)

Yale University Practice Differences: See above under 630.1

2. The investigator should be 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. (ICH-GCP 4.1.2)

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

4. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements. (ICH-GCP 4.1.3)

5. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies). (ICH-GCP 4.1.4)

6. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. (ICH-GCP 4.1.5)

630.5 Investigator Responsibilities

In order to satisfy the ICH-GCP (E6) requirements, Investigators who conduct research involving human subjects must satisfy the following:

1. During and following a subject’s participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial (ICH-GCP 4.3.2)

2. The investigator informs a subject when medical care is needed for other illnesses of which the investigator becomes aware (ICH-GCP 4.3.2)

3. The investigator should follow the trial’s randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial 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) (ICH-GCP 4.7)

4. It is recommended that the investigator informs the subject's primary physician about the subject’s participation in the trial if the subject has a primary physician an if the subject agrees to the primary physician being informed (ICH-GCP 4.3.3)

5. Although a subject is not obliged to give his or her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights (ICH-GCP 4.3.4)

6. Where allowed, the investigator may assign some or all duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or other appropriate individual who is under the supervision of the investigator and/or institution. (ICH-GCP 4.6.2)

7. The investigator, pharmacist, or other appropriate individual, who is designated by the investigator and/or institution, should maintain records of the product’s delivery to the trial site, the inventory of the site, the use by each subject, and the return to the sponsor or alternative
disposition of unused product(s). 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 subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. (ICH-GCP 4.6.3)

8. The investigator permits monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority. (ICH-GCP 4.1.4)

9. The investigator ensures the accuracy, completeness, legibility, and timeliness of the data reports to the sponsor. (ICH-GCP 4.9.1)

10. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol. (ICH-GCP 4.11.2)

11. The investigator reports all serious adverse events (SAEs) to the sponsor except those SAEs that the protocol or other document (e.g., investigator’s brochure) identifies as not needing immediate reporting. The investigator follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB. (ICH-GCP 4.11.1)

12. The investigator should promptly provide written reports to the sponsor, the IRB, and where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial and/or increasing the risk to subjects. (ICH-GCP 4.10.2)

13. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension. (ICH-GCP 4.12.1)

14. If the IRB terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension. (ICH-GCP 4.12.3)

15. Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB with a summary of the trial’s outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution. (ICH-GCP 4.13)

16. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g. autopsy reports and terminal medical reports). (ICH-GCP 4.11.3)

Related Information

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidance for Good Clinical Practice – E6

AAHRPP Tip Sheet 11: Following the Guidelines of the International Conference on Harmonization – Good Clinical Practice (E6)” (9-11-2012)

ICH “Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance” (04/96)

100 PR 4, Department of Defense Supported Research

200 PR 1: Informed Consent for Research Participation: Competent Adult Participants

200 PR 2: Exception From Informed Consent (EFIC) Research

200 GD 2: Guidance on the Inclusion of Non-English Speaking Participants in Human Research

200 FR 1: Consent Template – Biomedical Research

200 FR 3: Sample Short Form Consent
Contacts

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<td>203-785-4688</td>
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<td><a href="mailto:hrpp@yale.edu">hrpp@yale.edu</a></td>
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Roles and Responsibilities

**Human Research Protection Program** (HRPP)

The Human Research Protection Program is responsible for oversight of human research protection through ongoing education, monitoring, and evaluation of all parties involved in the conduct of human research.

**Human Investigation Committee** (HIC)

The HIC I, HIC II, HIC III and HIC IV serve as the four Institutional Review Boards or IRBs for biomedical human research conducted at Yale University.

**Human Subjects Committee** (HSC)

The HSC serves as the Institutional Review Board for social, behavioral and educational human research at Yale University.

Revision History

11/4/2014
01/30/2015