Principal Investigator Responsibilities For Both Sponsor and Investigator-Initiated Studies

The Nuremberg Code

1946-1947

20 physicians from Nazi Germany tried for murder, torture and other atrocities committed in name of medical science

Resulted in the 10 Point Nuremberg Code which focuses on the ethical treatment of humans in non-therapeutic research, the elements described the cornerstone for the guidelines we have today.

- Voluntary Consent
- Scientifically sound design without alternatives
- Designed with preclinical knowledge and understanding of natural history
- Conduct avoids all unnecessary physical or mental suffering and injury
- No experiments where there is risk of death or disabling injury
- Degree of risk should not exceed the benefits
- Proper planning and facilities available to protect the patient
- Conducted by scientifically qualified persons
- Right to withdraw consent
- Obligation of the scientist in charge to stop the study if continuation likely to result in injury, disability or death to the patient

The Helsinki Declaration

Adopted by the 18th World Medical Association General Assembly in Helsinki in June 1964 and amended periodically

- Last amended in 2004
- The WMA developed the Declaration as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects

“It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.”

“At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it”

The Belmont Report

In 1979 the United States, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote:

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

Three Basic Principles:

- **Respect for persons**
  - Individuals as autonomous agents
  - Persons with diminished autonomy are entitled to protection
- **Beneficence**
  - Do not harm
  - Maximize possible benefits and minimize possible harms
- **Justice**
  - Fair distribution of the benefits and burdens of research (equitable)
  - Inclusion of Women, Minorities and Children in research

International Conference on Harmonization (ICH)

Established in 1990 to maintain a forum between regulatory authorities and the pharmaceutical industry in the European Union, USA and Japan in order to ensure a more timely introduction of new medicinal products and their availability to patients

ICH Guidelines

- The objective is to increase international harmonization of technical requirements to ensure that safe, effective and high quality medicines are developed and registered in the most efficient and cost-effective manner
- To promote public health, prevent unnecessary duplication of clinical trials in humans and minimize animal testing without compromising safety and effectiveness.

Principal Investigator (PI)

According to FDA Code of Federal Regulations Title 21 (21CFR 312.3)

- An individual who actually conducts a clinical investigation
- The person under whose immediate direction the investigational drug is administered or dispensed to a subject
- The leader of the team of investigators
- Usually a physician, although a Pharm D or PhD can be PI as long as a physician is a co-investigator

PI Eligibility

- Based on the assumption that the PI has sufficient training and experience for the responsible management of a sponsored project
- Requires a background that includes training, knowledge and familiarity of all the issues and areas of expertise related to the project or protocol

Key Responsibilities of the Principal Investigator

- Provides investigator qualifications and agreements
- Ensure protocol compliance
- Ensure initial and ongoing review by a duly constituted REB
- Determines adequate resources are available to conduct the study
- Manages the medical care of subjects
- Protects the rights and welfare of subjects
- Ensures validity of the Data reported to the sponsor
- Ensures documentation of study-related procedures, processes and events
- Ensures the proper use and storage of investigational agents
- Directs Site operations (includes participating and permitting monitoring visits and regulatory audits)
- Maintains Professional and Technical Knowledge

Responsibility of the PI

By signing the Qualified Investigator Undertaking (QIU) for Health Canada and/or the FDA 1572 the PI:

- Agrees to comply with the regulations of CFR Title 21 which states the PI assumes the responsibility of the **entire** conduct of the study at his/her site
- Is accountable for everything that happens during the course of the study

Qualified Investigator Undertaking (Health Canada QUI Form)

An undertaking must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified. The complete undertaking must be retained by the clinical trial sponsor for a period of 25 years.

Qualified Investigator Undertaking (Health Canada)

PI certifies that:

Physician or dentist and a member in good standing of a professional medical or dental association as defined in Part C Division 4 of the Food and Drug Regulations

Will supervise the medical care and medical decisions respecting this clinical trial at this site

Will immediately on discontinuation of the clinical trial by the sponsor, in it's entirety or at a clinical trial site, inform both the clinical trial subjects and the Research Ethics Board for this site of the discontinuation, provide them with the reasons for the discontinuation and advise them in writing of any potential risks to the health of clinical trial subjects or other person

FDA 1572 (Statement of Investigator)

Commitments:

Agree to conduct the studies in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor except when necessary to protect the safety, rights or welfare of Subjects

Agree to personally conduct or supervise the described investigations

FDA 1572 (Statement of Investigator)

Agrees to inform any patients or any persons used as controls, that the drugs are being used for investigational purposes and will ensure that the requirement relating to obtaining informed consent in 21 CFR Part 50 and REB review and approval in 21 CFR Part 56 are met

Agrees to report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64

Have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug

FDA 1572 (Statement of Investigator)

Agrees to ensure that all associates, colleagues, and employees assisting in the conduct of the studies are informed about their obligations in meeting the above commitments

Agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.62

Agrees to comply with all other requirements regarding the obligations of clinical investigations and all other pertinent requirements.

FDA 1572 (Statement of Investigator)

To ensure that the REB complies with the requirements of 21 CFR Part 56, the PI will be responsible for the initial and continuing review and approval of the clinical investigation.

Also agrees to promptly report to the REB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

Will not make changes in the research without REB approval except where necessary to eliminate apparent immediate hazards to human subjects

Further Responsibilities of PI

Pre-study

To review the protocol and ensure the study budget includes **all study related activities** including patient expenses allowed by REB

Coordinate contract, REB submission, training of staff

Attend Investigator Meetings and Initiation Meetings

Ensure patient population exists for study inclusion/exclusion criterion

Develop enrollment strategies with co-investigators and study staff

Fill out financial disclosures accurately

Clinical Trial Recruitment

Efficient, effective, inclusive and consistent enrollment in clinical trials

Barriers to Enrollment

Lack of awareness about the clinical trials that may benefit patients

Protocol or eligibility criteria that are too rigid

Lack of time/person power to explain the clinical trial to patients

Successful Strategies to Enrollment

Physicians are considered a “trusted source” of information and patients are more likely to participate in a clinical trial if their physician suggests referral to a clinical trial

Advertisement

Dedicated health care professional to identify potential candidates (dedicated recruiter)

Positive discussion between doctor and patient is key in eliminating preconceptions regarding clinical trial participation

Good Clinical Practice

PI is responsible for conducting the study in accordance with the standards of Good Clinical Practice (GCP)

GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials

GCP establishes the conduct of the study according to the protocol and protecting human subjects at all times

More Responsibilities of PI

PI is responsible for assigning personnel to perform various study related activities (from Co-investigators to study coordinators) as specified by the sponsor

PI is responsible to ensure that all designated personnel are trained to perform study related activities

PI is responsible to ensure that GCP/ICH guidelines are followed and documented

Ultimate Responsibility of PI

The PI will protect the safety and well-being of all participants in the clinical study at all times

Investigator-Initiated Studies in Canada

Health Canada regulations must be followed. Division 5 clinical trial guidelines detail Investigator Responsibilities

"The Qualified Investigator is responsible for the conduct of the clinical trial at the trial site. Tasks delegated from Qualified Investigator to others (Sub-Investigator, Clinical Research Coordinator, Pharmacist and others) should be documented, signed and dated by the Qualified Investigator and the person to whom the functions were delegated. The extent of delegation should be clearly stated; e.g. who will be responsible for assessing, and reporting of serious adverse drug reactions / serious unexpected adverse drug reactions, and the reporting of these reactions within the specified time limits. Tasks not specified as being delegated are deemed to remain under the direct responsibility of the Qualified Investigator."

“The informed consent forms shall include a statement to relay that regulatory authorities such as Inspectors of Health Canada will be granted direct access to subjects' original medical records for verification of compliance (reference GCP 4.8.10(n)). This statement, when signed by subjects enrolled in a clinical trial, provides access to original medical records for inspection by Inspectors.”

The Qualified Investigator should ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site. The essential processes should be described in a standard operating procedure (SOP) and evidence of satisfactory training of personnel involved in these processes should be documented.

"All records created during the conduct of clinical trials are all subject to inspection. Source documents, including signed informed consent forms, medical records, office charts, laboratory reports, X-rays, subject diaries, appointment / scheduling records, adverse events and drug reactions records, pharmacy records, and other essential documents including communications with Sponsors and Research Ethics Board, qualifications and evidence of training of staff involved in the trial are all examples."

These records should be kept in a secure location to maintain their integrity and confidentiality. Access to these records should be restricted to personnel who have been appropriately trained in the management of these records.

“Sponsors of clinical trials are required to obtain an approval of a properly constituted Research Ethics Board prior to the initiation of a trial. Sponsors are also required to have an REB approve amendments, informed consent forms and conduct periodic reviews of the trial. The Board should also attest that it carries out its functions in a manner consistent with good clinical practices”

For an Investigator-initiated study, the sponsor may be the university, hospital or a research facility. An REB is required.

Essential Documents

Investigator-initiated studies must keep essential documents not only as required by investigator but also as sponsor. Trial Master File (TMF) essential documents and Investigator Study File (ISF) essential documents must be kept by the PI in investigator-initiated studies

Essential documents include:

- Investigator's Brochure/Product monographs
- Signed Protocol, Amendments, and sample CRFs
- Informed Consent Form, information given to subjects, signed informed consent forms
- Advertisements
- Financial documentation
- Signed Agreement (investigator and institution)

Essential Documents

- REB submissions, approvals, correspondence, annual reports from PI, close out report from PI
- REB Membership lists
- Health Canada notification, correspondence
- CV's of PI, sub-investigators and study staff
- Laboratory certifications, normal range values

Essential Documents

- Investigator Product information, labeling, packaging, product inventory logs, certificate of analysis, drug accountability, record of drug destruction
- Randomization list, decoding procedures
- Site initiation report, monitoring reports, close-out reports (if applicable)
- Source documents, completed CRFs
- SAEs and SUADRs

Essential Documents

- Subject Screening logs, Subject ID list, Subject Enrollment log
- Delegation of Duties and signature log
- Record of retained body fluids/tissue samples
- Final Clinical Study Report

Clinical Trial Monitoring
(HC GCP Consolidated Guideline ICH Topic 6)

5.18.1 Purpose
The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/ or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

Clinical Trial Monitoring (HC GCP Guideline)

- The Sponsor is responsible for creating the Monitoring Plan. In an Investigator-initiated study where the PI may also be acting as sponsor, the PI would be responsible to develop the Monitoring Plan.

- The monitor follows the Monitoring Plan set out by the Sponsor (PI or pharmaceutical company or CRO) and amendments are made to the Monitoring Plan throughout the study as necessary, i.e. change in frequency of monitoring visits if necessary, revision to when drug is reconciled and destroyed.

- The Monitoring Plan can be a living documents and new versions created and signed by sponsor (or PI if investigator-initiated study)

- The PI is responsible for the study and should attend at some point during or at end each monitoring visits to discuss Monitor findings. If not possible, the PI should try to attend the next monitoring visit.

- PI is responsible to act on findings of the Monitor in follow-up to the monitor visits.

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- Protects the rights and welfare of subjects
- Ensures validity of the Data reported to the sponsor
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- Maintains Professional and Technical Knowledge