Clinical Research Professional Certification Program

Chapter 12

Informed Consent

CRA SCHOOL

Chapter 12: Informed Consent

"Everyone hears only what he understands"

Johann Wolfgang von Goethe

"Without 'consent' in any human interactions, there's an ethical violation"

Henry Johnson Jr

Objectives:

By the end of this chapter, the student will be able to:

- Understand the importance of informed consent as a **protection** for the clinical trial subject.
- Be aware that informed consent is a process of **communication**.
- Identify the required **elements** of informed consent.
- Understand the process for **obtaining** informed consent.
- Know what situations are **exempt** from informed consent.

Introduction

When an individual first realizes that they may be eligible to participate in a clinical trial, they may feel worried, excited or hopeful for a change in their health. They may also be in a situation

where unscrupulous investigators could use **coercion** to convince them to join the trial, just to fulfil their enrollment goals. However, enrollment in a clinical trial should be based on presentation and evaluation of **facts**, not based on emotion. The prospective subject must be able to understand **why** the trial is being conducted, what the trial **procedures** will be and what their individual rights and **obligations** to the trial will be, if they agree to join. To ensure that this is the case, clinical trial recruitment relies on the **Informed Consent** (**IC**) process.

IC is the process through which a person learns about the **objectives**, **risks**, **potential benefits**, **procedures** and **expectations** that will be made of them if they commit to entering a clinical trial.

There are 2 key concepts within the IC process:

Comprehension - the potential subject must fully **understand** what it is that they are committing to, **before** they agree to participate and before their eligibility to participate in the study is evaluated. To achieve this, everything should be explained in easy-to-read, non-technical language.

Voluntary action- the commitment to participate must come **from the subject alone**, without any **persuasion** or pressure from the clinical trial team, or anyone else.

Along with the protocol approval by an independent ethical review board (IRB), IC is the second most important tool to **protect** the rights and wellbeing of clinical trial subjects.

A Brief History of Informed Consent

As with much concerning the ethical approach to clinical research, informed consent has its roots in the **Nuremberg Code**, the **Declaration of Helsinki** and the **Belmont Report**. These enormously important documents established and refined the ways that we think about involving human participants in biomedical research. Previously, it was often reasoned that the "advancement of science" or the possible benefit to the general population was sufficient justification for experimentation on individuals. These landmark publications brought the **rights** and **protection** of the individual research subject to the forefront of consideration.

The idea of *giving consent* was first recognized in the Nuremberg Code as being absolutely essential for human research, in view of the forced and abhorrent experimentation conducted by the Nazis on unwilling prisoners. The civilized world decided that, never again would unwilling and unsuspecting people be tricked, forced or otherwise allowed to take part in human experimentation unless they were **willing** to do so, they **understood** what it was that they were undertaking and were **free to withdraw** from the experimentation whenever they

desired, with **no fear of negative consequences**. (Negative consequences, in the modern perspective, could mean a subsequent inferior level of care from a physician.) These basic, fundamental principles provide the ethical foundation for interactions with individuals considering participating in clinical research.

In 1982 the WHO ***Council for International Organizations of Medical Sciences*** (**CIOMS**) released the **International Ethical Guidelines for Research Involving Human Subjects** to extend these ethical ideals globally and to promote the same ethical foundation for research in any country. In 1996, the International Conference on Harmonization's Guideline for Good Clinical Practice (**GCP**) was established to harmonize and protect the rights of research subjects, including detailed requirements governing informed consent. GCP is now a recognized global standard for the clinical trial industry. (Section 4.8 of GCP, *Informed Consent of Trial Subjects*, can be found in Appendix 1.)

What is Informed Consent?

GCP Definition

1.28 Informed Consent:

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the

subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

In section 2.9, GCP states:

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Many people mistakenly believe that IC is just a physical **form** that is signed before a clinical trial can begin. While it is true that the form is the most visible part of IC, it is important to understand that IC is a **process** that starts when the potential subject first meets the study team and **continues** throughout the trial. It is a process whose goal is to keep the subject informed, so that they will always be able to make **informed decisions** about their participation. **IC is an ongoing process of communication** where the clinical trial subject is free to walk away from the trial commitments at any time. Any time that new, relevant information becomes available, the IC form must be updated and re-approved by the subject.

From the FDA site:[1]

[1] https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials

FDA believes that obtaining a research participant's **verbal or written** informed consent is only part of the process. Informed consent involves providing a potential participant with:

- **Adequate information** to allow for an informed decision about participation in the clinical investigation.
- A **level of explanation** that facilitates the potential participant's **understanding** of the information.
- **An appropriate amount of time** to ask questions and to discuss with family and friends the research protocol and whether you should participate.
- **Continued provision of information** as the clinical investigation progresses or as the subject or situation requires.

To be effective, the process must provide **sufficient opportunity** for the participant to **consider** whether to participate. (21 CFR 50.20). The FDA insists that participants are allowed **sufficient time** to consider the information and are provided opportunity to **ask questions** and have those questions answered. They must be allowed time to consult with their families and friends, if they wish. The investigator (or other authorized staff who are conducting the informed consent interview) and the participant should exchange information and **discuss the contents of the informed consent document.** This process must occur under circumstances that **minimize the possibility of coercion or undue influence.** (21 CFR 50.20.)

When does Informed Consent Occur?

IC must commence as soon as the potential clinical trial subject meets a member of the study team. It must continue until the trial is completed or subject participation has ended. If any **changes** occur in the protocol, the subject must be informed as soon as possible and given a suitable opportunity to consider what these changes mean to their participation and health. Furthermore, the **informed consent form** (**ICF**) originally signed by the subject must be **amended** to include the protocol changes that may affect subject's safety or **willingness** to continue in the study. The amended protocol and ICF amendments must be **approved** by the IRB before the amended ICF is presented to the subjects.

Clinical trial source documents must show that IC was procured **prior** to the start of the study. Failure to obtain IC **prior** to subject participation in the study constitutes a **major protocol violation**. This is key information that sponsor's trial monitor will verify first during visits.

Who is Responsible for Creating and Implementing Informed Consent?

The IC document (**ICD**, or IC Form**; ICF**) will usually be created by the **sponsor** and provided to the **investigator** at the site. Logically, the sponsor wants to be *absolutely sure* that the IC documents are precisely what is required. They do not want to risk having small (or large)

errors slip through and create **legal problems**. In some cases, however, the investigator may be responsible for creating it themselves, especially if he/she is a **sponsor-investigator**.

After the IC document has been approved by the IRB/ethics board, the **investigator**, or other specific study personnel designated by the investigator, is/are responsible for discussing the content of the form with the prospective trial subject. If the subject agrees to participate, they must **sign and date** the IC form. This is a critical legal requirement. As mentioned, **the date** must show that their decision preceded any trial activities, and no subjects can be recruited until after the IRB has approved the entire IC process.

The Informed Consent Form

Although we describe IC as a process, the proof of **willingness** to participate on the part of subject must be **documented** physically on the **IC form (ICF).** This form is important to the sponsor and investigator as **legal proof** that the due process has been followed. It is important to the subject, as it provides a detailed **description** of their commitments to the clinical study and it is a reminder about why the study is being run. Three copies of this form are made.

A **Patient (or Participant) Information Sheet** (**PIS**) is often included as part of the IC documents. The PIS explains to the subject, in simplified language that is clear and understandable, **why** the

trial is being done and **what it involves**. It should include all relevant trial-related information for the subject. The PIS is an **educational tool**, not a legal document or an agreement but it also needs to be approved by the IRB to make sure that it doesn't contain misleading information.

The IC form must be **signed and dated by the subject** (or their legally authorized representative) and by the person performing the informed consent. It must not be signed by anyone else! The subject **keeps one copy** and the original copy stays at the site, separate from the other study files. It should not be stored with the patient's hospital files/medical records.

The IC form is valuable to the study and contains confidential information. It should therefore be kept in a **locked** filing cabinet or room, to limit access only to those authorized to work with the study documents.

Only **the most recent**, IRB-approved IC form may be used during a clinical trial. Any **change** to the IC document must be approved by the IRB prior to its use.

The IC document must be **specific** to the clinical trial in question. In other words, it cannot be a generic, or standard form containing general information. It must explain very specifically what the trial is investigating and how it will be done.

The ICF must fulfil certain general **requirements**:

- It must provide a detailed account of the protocol **procedures**, including all trial activities in which the participant will be taking part. Subjects must fully understand what activities they will be expected to undertake. For example, the ICF must state the **tests** they will undergo and the frequency of **visits** to the site, what **discomforts** should the participant anticipate.
- It must present all information in a way that will be understood by the participant regardless of their level of educational. The entire presentation of the relevant information must be designed to maximize comprehension.
- All **regulatory requirements** must be met (e.g. 21 CFR 50 in the USA).
- The subject must understand that they are **free to leave** the trial at any time.
- It must state that the subject should not be asked to waive legal rights or release the investigator or sponsor from liability for negligence.

Signed IC documents must be kept for **at least 2 years** after the last approval of a marketing application in an ICH region (and until there are no pending marketing applications), or for at

least 2 years following the halt of clinical development for the investigational product. Depending on the institutional policy or country it may be longer, for example, 15 years in Canada. In the USA, the forms must be kept for 6 years if **protected health information** (PHI) is used. Following the 2-year period, the documents may be **destroyed** in an acceptable manner (e.g. by shredding or burning, **not** simply by recycling), although usually they are kept much longer "just in case".

Comprehension of the Informed Consent Process

The IC process must use language that will be understood by the subject considering participating in a clinical trial (or their **Legally Authorized Representative; LAR**)[2]. This must be done carefully, as a clinical trial often involves complex science and requires a long explanation.

The trial team must understand that any clinical research trial will involve subjects from a wide range of backgrounds. Education level and intellectual capacity will vary widely. In addition, the study may be in a language that is not their mother tongue. The subject may have no understanding of scientific concepts, or may have trouble reading or hearing.

END OF SAMPLE TEXT (P. 12 OF 74)

[2] Also called Legally Acceptable Representative.