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SHORT COMMUNICATION

Informed Consent: A Mandatory Step in Clinical Trials.

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ABSTRACT:

Voluntary written consent given by potential subjects to participate in a clinical trial is known an informed consent. The informed consent process is designed keeping in mind the safety, benefits and rights of the research participants. Participants should sign the informed consent form only after they have thoroughly read and understood the content given in informed consent form and they should be able to utilize all the benefits and rights mentioned in the form. Research team should make an attempt to clarify the potential subjects about the difference between Clinical trial and Pharmacotherapeutics. This article contains the history, key elements, basic requirements, influential factors and obstacles of informed consent process.

INTRODUCTION:

A number of new drugs are being marketed in India and abroad through Clinical trials. India has become a hub for testing of new drugs on humans which are being invented in abroad. Now-a-days research involving human subjects poses some complex ethical issues. The informed consent is such an ethical issue which comes into picture when a drug is being tested for the first time in human beings. *The informed consent process is designed to inform the subjects of the risks, rights, and benefits of participation in a clinical research trial. Informed consent, while not always necessary, is a critical component ethical research involving human subjects*. [1]

Informed consent for a clinical trial is not just signing a consent form but it comprises of two important components: a document and a process. The informed consent document gives the summary of a clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives treatments) and explains your rights as participant. It is a platform on which on which informed consent process stands, which starts with discussions between the potential subjects and the research team. [2]

HISTORY:

Experimentation involving human being had been performed in an unethical and even criminal fashion. In early twentieth century, the ethical guidelines for performing experimentation were related only to the clinician's need to adhere to acceptable medical standards in designing and conducting clinical trials. The issue of patient's agreement was never addressed in those days. At the end of the World War II, the Nuremberg War crimes Tribunal found 18 out of 25 accused medical men guilty of war crimes of a medical nature against involuntary human subjects. [3] A code of ethics was subsequently developed to curb human abuse (the Nuremberg code- the first international code of human experimentation ethics) to address the question what is ethical, moral and legal in human experimentation. Even after this incidence, physicians, particularly in United States, did not stop using underprivileged groups for experimental purposes. In one instance, a project conducted in Willow brisk Residential School for mentally subnormal children in united states Island, New York, deliberately infected groups of new admissions with viral hepatitis in an effort to find an effective vaccine against it. Similar unethical research on retrolental fibroplasia included a set of premature infants who were given high concentration of oxygen for two weeks, causing a number of infants to go permanently blind. [4]

Such investigations indicated that some principles of control must be laid down to restrain investigations from excess of zeal in experimenting with human subjects and thereby, to protect the innocent from the fanatics.

DECLARATION OF HELSINKI -1964:

At the 18th World medical assembly in Helsinki, Finland, the World Medical Association adopted 12 principles to guide physicians on ethical considerations relate to biomedical research denoted as Declaration of Heisinki-1964. It emphasizes the distinction between medical care that directly benefits the patients and the research that may or may not provide the direct benefit.[2] The Declaration of Helsinki on informed consent in the context of medical research combined with professional

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care (Clinical research) states, "In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort may entail. She/he should also be informed that he/she is at liberty to abstain from participation in the study and that he/she is free to withdraw his/her consent to participation at any time. The physician should then only obtain the subject's freely given informed consent, preferably in writing. Even though, the reasons sufficiently valid to override the ethical obligation to obtain informed consent are not suggested in the declaration. However, it does allow physicians, sometimes to use subjects without giving informed consent. As it further says, "If physicians consider it essential not to obtain informed consent, the specific reason for this proposal should be stated in the experimental protocol for transmission to the ethical committee." [5]

The National Commission for the protection of the human subjects of Biomedical and Bahaviour Research issued the Belmont Report in 1979 after The National Research act in 1974.

THE BELMONT REPORT: [2]

Ethical Principles and Guidelines for the protection of Human Subjects of Research. The report sets forth the three principles underlying the ethical conduct of Research

1. ***Respect for persons:*** *Recognizing the autonomy and dignity of individuals and the need to protect those with diminished autonomy (i.e. impaired decision making skills), such as children, the aged, and the disabled*
2. ***Beneficence:*** *An obligation to protect persons from harm by maximizing benefits and minimizing risk*
3. ***Justice:*** *Fair distribution of the benefits and burdens of research*

In 1991, Federal Policy for the protection of human subjects was adopted to ensure a uniform system of protection in all federal agencies and departments that conduct research.[2] In the year 2000, The Indian council of Medical Research (ICMR) laid down comprehensive ethical guidelines within which biomedical research should function.[6] According to Code of Federal regulations (CFR) Titles 21 and 45:21 CFR 50 and 56, the Food and Drug Administration (FDA) Regulations, Clinical trials must be "*well-designed, well –conducted, performed by qualified investigators and conducted in accordance with ethical principles acceptable to the world community*.[1,7]

Clinical Research guidelines require that every adult volunteer must agree to participate in writing before he/she can enroll in a clinical trial. [7] A legal and ethical prerequisite for conducting clinical trials is that individual give voluntary informed consent to participate in them. [8] Informed consent is the process, dialog and invitation for the fully informed patient to participate in choice about his/her health care and is simply memorialized in the signature or mark. It originates from legal and ethical right of the patient to direct what happens to his/her body and from ethical duty of the physician to involve patient in health care decisions. Valid consent means that patient is competent to make decision and that consent is voluntary. [9]

KEY ELEMENTS OF INFORMED CONSENT:

There are four key components of Informed consent: Information, Comprehension, Voluntariness and decision making capacity. [7,10]

Information: One of the important components of informed consent is that potential subjects should be provided with all the available information that is relevant to a decision concerning participation. Practically, informed consent forms should be designed in a way, which a thoughtful layperson would consider relevant to such a decision. As a minimum, federal regulations identify eight different type of information thought to be provided to potential subjects, such as the research question, study procedure, nature and purpose of the study, alternative treatments, a statement offering the subjects the opportunity to ask questions, likely burdens and benefits and to withdraw among others. The information in the consent form should be in language understandable to the study subject and should minimally use technical words. Difference between clinical care and clinical trial must be clearly explained to them and should be informed well about their enrollment either in drug or placebo arm of the trial. [7, 10]

Comprehension: It's not just enough to provide the information but there should be substantial understanding of the information to the potential subjects. It requires a level of comprehension or appreciation of information that is adequate for decision making. Potential subjects must be given ample time and space to discuss their doubts with knowledgeable research team member, their family, friends and family doctor. Special attention is required for those who cannot give or refuse consent for themselves like children, people with dementia or stroke, critically ill patients. In such cases proxy consent can be considered with a person who can understand well the situation of incompetent person. [7, 10]

Voluntariness: Informed consent is supposed to be valid only if it is voluntarily given. It means that informed consent is one that freely given, representing the determination of subject's own desire to participate and it

is not controlled by anyone other than the subject. Participants should make a choice whether to enter into medical research or not after understanding all the benefits and risks associated with the research.[7,10] *Participants should not be subjected to "force, fraud, deceit, duress or coercion"*.[11]

Decision making capacity: Informed consent requires that potential subjects should have the capacity to make a decision about participation. They must be able to assess the possible risks and benefits of participation in accordance with their personal interests. Sometimes, professional pressure can lead researchers to underestimate the inconvenience and hazards which participants may face, misleading volunteers in the process. Volunteers must have accurate and detailed information about potential risks in order to protect themselves. If the potential subjects do not have capacity to make an authentic decision about research participation the proxy consent may be a substitute. Ideally, proxy consent should be a legally authorized representative (LAR) who can fulfill the absence of the potential subject. [7, 10]

BASIC REQUIREMENTS OF INFORMED CONSENT: [1]

The process of obtaining informed consent from subjects is a critical point of entry for research participants. There are certain basic requirements of informed consent document like:

1.Informed consent should be taken from the subjects or subject's legally authorized representative (LAR) without any undue influence

2.The information contained in the informed consent document should be in a language understandable to the subject.

3.The informed consent document (ICD) should explain the purpose and duration of study along with the procedures to be used in the study.

4.The ICD should also include the description of foreseeable risks, benefits, alternative treatments and confidentiality of records.

5.It must be mentioned in ICD that participation is voluntary and the subject is free to withdraw from study at any time and in such case, there will not be any testing or evaluation.

6.The ICD must identify a person to whom subject can contact in case of any query regarding research/subjects' right/ research related injury.

7.Potential subjects should be informed well about whether any medical treatment or compensation is available in case of injury.

8.Content given in the advertisement for clinical study should be consistent with the information provided in the ICD.

9.The advertisement should state that the study involves research and indicate that the drug or device is investigational or experimental.

10. No claim should be made that drug or device is safe or effective for the purpose under research.

FACTORS INFLUENCING INFORMED CONSENT PROCESS:

It has been suggested that informed consent process is an interactive and dynamic process and there are many factors influencing the decision of a study subject to participate in a trial. Such factors include socioeconomic background, cultural traditions, level of education, known language, rapport with clinical researchers and their emotional status. Emotional status plays an important role in informed consent process, especially when a patient is diagnosed with some life threatening illness[12,13] Any previous participation in a clinical trial gives a positive feedback to the subject to participate again in the study.[14]

HOW INFORMED CONSENT PROCESS CAN BE SUCCESSFUL:

The informed consent process starts when a potential subject, after screening, is first approached for inclusion in a clinical trial. The informed consent should be taken in a peaceful and private atmosphere, where subject has enough time to analyze the informed consent document and to clear his/her doubts about the research. Researchers should properly introduce themselves and should explain the purpose of subject's participation in the trial. The informed consent document should be in simple language which is understandable for study subjects. [15] When study co-coordinators and research subjects speak and understand different languages, it can cause misunderstanding in the clinical study. [13] In such cases, informed consent document should be translated in the language, the potential subject understands. Moreover, the subject's understanding can be enhanced by using graphics, video, or any other possible means. Subjects should be encouraged to ask more and more questions and can be allowed to carry the document along with them. Clinical researches should not present overly positive or negative picture of clinical trial. [15]

PROBLEMS WITH INFORMED CONSENT PROCESS:

There are some major challenges for study participants and research staff in the informed consent process. Some of the issues are:

- *Subject's hesitation to ask detailed questions*

- *Variable presentation of the content*
- *Difficulty verifying the subject's comprehension*.[16]

It has been estimated that some of the subjects do not read the consent form before signing and high percentage of the volunteers don't understand the harms which can be associated with the study and they don't know what to ask? Moreover, the study participants are not really aware of the difference between medical treatment and clinical trial. [17, 18, 19]

In Conclusion, informed consent process has become a mandatory process in clinical research before enrollment of subjects in any clinical trials. The main purpose of this to reserve the safety and rights of study participants provided the participants know, how to utilize that. No doubt, the first time use of any new drug in human is a risky task, as described by Getz and Borfitz "*Clinical Research might best be likened to a journey down a new, unexplored and potential dangerous path",*[20] but informed consent process, to large extent, helps the subjects to compensate for all the possible risks that can happen with clinical research.

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