

Informed consent: Issues and challenges

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ABSTRACT

Informed consent is an ethical and legal requirement for research involving human participants. It is the process where a participant is informed about all aspects of the trial, which are important for the participant to make a decision and after studying all aspects of the trial the participant voluntarily confirms his or her willingness to participate in a particular clinical trial and significance of the research for advancement of medical knowledge and social welfare. The concept of informed consent is embedded in the principles of Nuremberg Code, The Declaration of Helsinki and The Belmont Report. Informed consent is an inevitable requirement prior to every research involving human being as subjects for study. Obtaining consent involves informing the subject about his or her rights, the purpose of the study, procedures to be undertaken, potential risks and benefits of participation, expected duration of study, extent of confidentiality of personal identification and demographic data, so that the participation of subjects in the study is entirely voluntary. This article provides an overview of issues in informed consent: The obligations of investigator, sponsor and Institutional Review Board to protect rights and welfare of human research subjects. It discusses about the basic elements of informed consent and the process to be followed while obtaining informed consent. Some of the circumstances under which informed consent can be waived and ethical challenges faced by physicians in obtaining informed consent from subjects are also highlighted in this article.

Key words: Human subjects, informed consent, institutional review board

INTRODUCTION

For a drug to get approved and enter into the market it has to prove its safety and efficacy in clinical trials. Clinical trial is a term used to describe all research related activities, which use human being as subjects. As no individual has right to infract fundamental rights of another person for the sake of fulfilling his own purpose, so an important tool called "informed consent" came into existence.

The informed consent is described in ethical codes and regulations for human subject's research. The goal of the informed consent process is to provide sufficient information to a potential participant, in a language which is easily understood by him/her, so that he/she can make the voluntary decision regarding "to" or "not to" participate in the research study.

Conventionally informed consent is thought to be in terms of the documents signed and dated by participants, setting forth the purpose, benefits, risks and other study information necessary to allow the participants to make an informed and voluntary decision to participate in the clinical study. In reality, informed consent is the process that applies to each communication to participants, commencing with the subject recruitment material and the initial telephone screening of potential subjects through the conclusion of the study. It also describes the obligation of the investigator to inform the subject about personal benefits and risk, individual faces in study.

Informed consent is not only required for clinical trials but is an essential prerequisite before enrolling each and every participant in any type of research involving human subjects including; diagnostic, therapeutic, interventional,

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bioequivalence, social and behavioral studies and for all research conducted domestically or abroad. Obtaining consent involves informing the subject about his or her rights, the purpose of the study, the procedures to be undergone, the potential risks and/or benefits of participation and alternative treatments available if any. Subjects in the study must participate willingly only after consenting based on the information given.^[1-3]

THE ORIGINS OF INFORMED CONSENT

Informed consent is a central tenet of research ethics involving human beings and has evolved into present shape over a period of time. The journey of informed consent is briefly described below [Tables 1-3].^[4-7]

Table 1: Evolution of informed consent

1947-The Nuremberg Code	Developed in response to the Nuremberg trials of Nazi doctors who performed unethical experimentation during World War II, the code was the first major international document to provide guidelines on research ethics. It made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if: Participants are able to consent They are free from coercion (i.e., outside pressure) They comprehend the risks and benefits involved. The code also states that researchers should minimize risk and harm, make sure that risks do not significantly outweigh potential benefits, use appropriate study designs and guarantee participant's freedom to withdraw at any time
1964-Declaration of Helsinki	World Medical Association in Helsinki, Finland adopted 12 principles to guide physicians on ethical considerations related to biomedical research. It emphasizes the distinction between medical care that directly benefits the patient and research that may or may not provide direct benefit. These guidelines were revised at subsequent meetings in 1975, 1983, 1989, 2000 and 2008
1979-The Belmont Report	The report sets forth three principles underlying the ethical conduct of research 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 Beneficence: An obligation to protect persons from harm by maximizing benefits and minimizing risks Justice: Fair distribution of the benefits and burdens of research The Belmont Report explains how these apply to research practices; for example, it identifies informed consent as a process that is essential to the principle of respect

Table 1: Contd....

1982-CIOMS guidelines	In 1982, the WHO and CIOMS created the International Ethical Guidelines for Research involving human subjects. Most recently amended in 2002, the goal of the guidelines is to support and help implement the ethical principles of the Helsinki Declaration "particularly in developing countries, given their socio-economic circumstances, laws and regulations and executive and administrative arrangements." The guidelines identify 26 separate items of information an investigator must provide to trial participants prior to obtaining their informed consent
1996-International Conference on Harmonisation-GCP	Guideline for GCP was developed by International Conference on Harmonisation to provide a unified standard for the European Union, Japan and United States of America to protect the rights and wellbeing of subjects involved in clinical trials and to facilitate mutual acceptance of clinical data by the regulatory authorities in these regions in the year 1996

WHO: World health organization, CIOMS: Council for international organizations of medical sciences, GCP: Good clinical practices

Table 2: Classification of informed consent

Classification ^[8,9]	
Consent	An adult subject, capable of giving permission to participate in a research study, can provide consent. The subject must be 18 years of age and competent to make the decision to participate
Parental consent/permission	When children/minors are included in research, the parent/guardian must sign a parental permission consent document. Some situations require permission from at least one parent, while other situations require permission from both parents. In some cases, it may be necessary to waive the requirement to obtain parental permission
Assent	Assent is a child's affirmative agreement to participate in research. If the subject is 7-17 years of age, assent must be obtained. The assent form must be written at the appropriate reading level of the youngest subject in the age range and use simple terminology
Verbal	Verbal consent still contains all elements of written consent; however, the participant is verbally read the elements and verbally agrees to participate
Short form	A "short form" is generally used when there is a language barrier and an IRB's approved consent is orally translated in the subject's native language

IRB: Institutional review board

Table 3: Informed consent and obligations

Informed consent and obligations^[10-12]	
Investigator	<p>Design informed consent form</p> <p>Ensure that consent form include all elements required by regional regulatory body, that is to be informed to enrolled subjects</p> <p>Submit the designed consent form to IRB for approval</p> <p>Make changes in the form as required by IRB</p> <p>Use IRB approved consent form to discuss and explain trial related risks, benefits and other aspects with the potential participant and if required, the participant's legal representative, before the trial begins</p> <p>Provide the potential participant, ample time and opportunity to ask questions about the trial and discuss it with relatives and family members</p> <p>Do not force or unduly influence a subject to participate or to continue to participate in a trial</p> <p>Obtain a signed and dated voluntary informed consent from participants if the potential participants decide to get involved into the study</p> <p>Inform the participant of their right to withdraw from the ongoing study at any time without penalty, repercussions or reason</p> <p>Keep subject informed about new findings of the ongoing trial, which may affect their decision</p>
IRB	<p>Identify omissions in the consent documents provided by the investigators.</p> <p>Ensure that information will be presented to prospective subjects in language they can understand</p> <p>Take special care to ensure that both oral presentations and consent forms are comprehensible to all subjects</p> <p>Suggest modifications to be made in the form if necessary</p> <p>Suggest investigator to employ devices such as audiovisual aids, tests of the information presented, or consent advisors, to enhance participant understanding about the study</p> <p>IRB may waive consent requirement under certain circumstances</p>
Sponsor	<p>The sponsor and the local site investigators are jointly responsible for writing a site-specific informed consent</p> <p>Confirming that informed consent is sought properly by investigator prior to research</p> <p>Ensure that the investigator use only IRB approved forms to consent volunteers</p>
Subjects	<p>Should properly understand all relevant aspects before signing the form</p> <p>Must comprehend the relevant information</p> <p>Feel free to clarify his/her doubts</p> <p>Should consent voluntarily</p> <p>Should be aware of his/her rights for participating in the study</p>
Regulatory bodies	<p>Audit investigator's site</p> <p>To ensure the quality and integrity of data obtained from clinical trials</p> <p>To protect the rights and welfare of trial subjects</p>

Table 3: Contd...

Record retention	<p>Maintaining custody of required records and the means by which prompt access can be assured</p> <p>Retention of records at the study site for 2 years following the date on which test article approved by FDA or date on which clinical trial terminated or discontinued by the sponsor</p>
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IRB: Institutional review board, FDA: Food and drug administration

BASIC ELEMENTS FOR WRITTEN INFORMED CONSENT DOCUMENTS

1. A statement that the study involves research;
2. An explanation of the purpose of research and the expected duration of the subject's participation;
3. A description of the procedures to be followed and identification of any procedures that are experimental;
4. A description of any foreseeable risks or discomforts to the subject, an estimate of their likelihood and a description of what steps will be taken to prevent or minimize them;
5. A description of any benefits to the subject or to others that may reasonably be expected from the research. Monetary compensation is not a benefit;
6. A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject;
7. A statement describing to what extent records will be kept confidential, including a description of who may have access to research records;
8. For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if research subjects are injured; where further information may be obtained and whom to contact in the event of a research-related injury;
9. Information on the amount of remuneration/compensation, if any, that will be provided to subjects;
10. An explanation of whom to contact for answers to pertinent questions about the research and the research subject's rights (include the clinical center's patient representative and telephone number);
11. A statement that participation is voluntary and that refusal to participate or discontinuing participation at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled.^[13]

REQUIREMENTS FOR OBTAINING INFORMED CONSENT

1. The investigator or a person designated by investigator must obtain informed consent
2. Informed consent must be obtained before non-routine screening procedures are performed and/or before any

change in the subject's current medical therapy is made for the purpose of the clinical trial

3. The subject/subject's legally acceptable representative should not be forced to sign on consent or participate/continue to participate in the trial
4. The subject/legally acceptable representative and individual obtaining consent must personally sign with date the form. The signature of the prospective subject/legally acceptable representative on informed consent document indicated that content of informed consent document has been adequately discussed and the subject/subject's legally acceptable representative freely gave the informed consent [Figure 1].^[13]

INFORMED CONSENT PROCESS FLOW

Notes to Flowchart

1. Source documents must reflect that consent was obtained before the start of study treatment and procedures
2. A copy of the signed consent form must be kept at the site

3. All versions of approved consent forms must be kept in the site study file; only the current Institutional Review Board (IRB) approved version may be used to consent new patients.^[14]

WAIVERS TO INFORMED CONSENT

- A. A waiver of informed consent under 45 Code of Federal Regulations (CFR) 46.116 (d)
- B. An alteration of consent under 45 CFR 46.116 (d)

An IRB may waive the requirements to obtain informed consent provided the IRB finds and documents that:

 - The research involves no more than minimal risk to the subjects;
 - The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - The research could not practicably be carried out without the waiver or alteration and
 - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

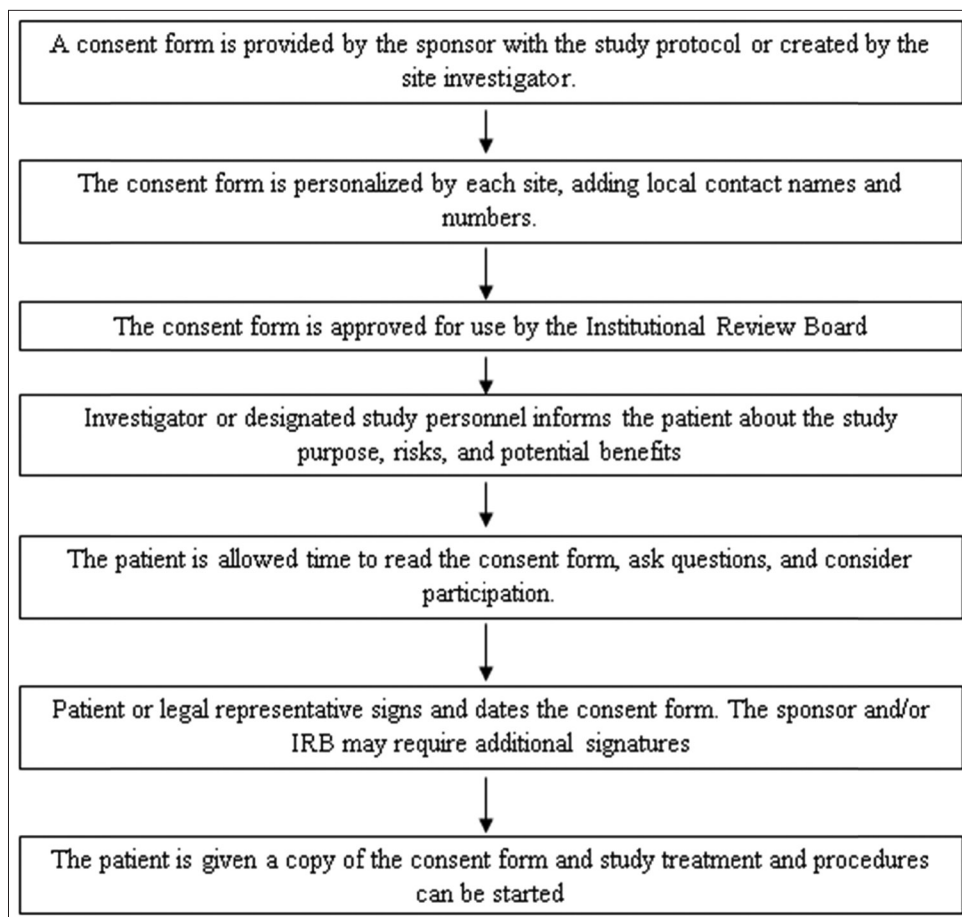


Figure 1: Flow chart regarding various informed consent processes

- C. A waiver of parent/guardian permission under 45CFR 46.408 (c)
- D. A waiver of assent under 45 CFR 46.408 because the minors are not capable of assent
- E. A waiver of assent under 45 CFR 46.408 because the research holds out a prospect of direct benefit that is available only in the context of the research.^[15]

CHALLENGES IN INFORMED CONSENT PROCESS

Language Barriers

It is assumed that the individual who signs the consent form does so with full understanding of what is stated on the consent form. However, it is very difficult to evaluate their viewpoint about trial since there is no established method to measure the level of understanding that a participant has about the information given. Thus, it can be assumed that there is a degree of misunderstanding that occurs. Misunderstandings can occur because of incorrect or inadequate language translations. Many individuals sign the consent form without being fully aware of what they are signing, which results in withdrawal of subject at later stages of ongoing clinical studies. Hence, the responsibility of researcher enlarges when a study is performed in multilingual subjects [Table 4].^[16]

Religious Influence

The informed consent process is designed to give every participant the liberty to decide whether to accept or refuse the recommended medical treatment. Sometimes their decision for participating in researcher projects is influenced by the religious beliefs. It is commonly observed that how the methodology of the experiment come into conflict with the rules of behavior set by a participant's religion.^[17,18]

False Expectations

Even when there are no language barriers or religious impediments to hinder the communication relationship between researcher and participant, misunderstanding can still occur due to participants false expectations of the experiment outcome. Some patient fear of being treated as mere "experimental model" for the studies while others refuse to take part because of historical evidences of clinical trial fraud and misconducts known to them.^[17,18]

Patient Perceptions

Most patients believe that, trials will put extra burden on them. They assume that the conventional treatment is best and they are afraid of the unknown side-effects of new treatment. Convincing and receiving an informed consent from such patient is most difficult. In some case disclosing too much information of the potential side-effects may unnecessarily scare the patient away

from a potentially life-saving or life-enhancing surgery or procedure.^[17,18]

Table 4: Barriers to participation in clinical trials

Theme ^[9]	Example
Lack of knowledge about clinical trials	Limited information about clinical trials "I can't participate because I don't know anything"
Fear (1) of new treatment	Uncertainties about side-effects Concern over quality-of-life in trials Fear of receiving placebo as opposed to actual treatment
Fear (2) of being treated as a test subject	Fear of being treated as "guinea pig"
Psychological issues	Denial or depression
Financial burden	Concern that insurance will not cover the treatment

Children

Where research involves children (under the age of 18) consent/permission has to be obtained from parents. If the child is above 7 years of age then "child assent" is also mandatory. It is arguable that children are capable of being partners in research and that they have rights to receive information, to be listened to, have their wishes and feelings taken into account and to give or withhold consent if judged competent to do so. Difficulty arises when parents give their consent while child refuses to assent.^[20]

Vulnerable People and Groups

Vulnerable groups include the person who is absolutely or relatively incapable of protecting their interests. Obtaining informed consent is critical when working with them, specifically with some groups like people with learning disabilities. There may be potential problems of understanding what the research is about, what their role in the research will be and how the research will be used. Hence, obtaining informed consent can be difficult and special care needs to be taken to develop the appropriate strategies for communicating the implications of involvement in research.^[21,22]

Indian Scenario

In countries like India, the clinical investigations are based on regional values and practices, the concept of disease as perceived through social values and power hierarchies in family of villages based on cultural systems. To get a meaningful and ethical informed consent in these settings become challenging due to differences in cultural values in western countries and local customs in developing countries including India. In a study by DeCosta *et al.*^[23] that was carried out in a village of Haryana state of India, the majority of respondents interviewed by them could decide on clinical trial participation after discussing with community members. Another important factor emerged from this study, which showed an implicit trust by respondents in the medical

system and ignorance about the information that should be known before consenting to be a part of the research study. These factors put a huge responsibility on the part of the investigator to get informed consent. The investigator must explain in most comprehensive and complete manner the risks involved in participating in the research study. Thus, investigator should have the patience to get informed consent from these subjects allowing them to discuss with other family and community members. The ethical principles of western countries require all adults to be the primary decision makers of their participation, which may not be applicable in Indian system, which is culturally and socially different from the western world.^[23] Another important aspect of informed consent arises in psychiatric clinical studies. As large numbers of psychiatry studies are conducted in India, these studies present complex and unique challenges in Indian context. These issues include risk of worsening of illness, use of placebo and validity of informed consent. The informed consent procedure requires patient to be of sound mind and in understanding the information presented and make a sound judgment regarding participation. Assessment of consent capacity may be difficult due to fluctuation in illness, which requires continued assessment of consent capacity. Thus, conducting clinical trials and obtaining informed consent for psychiatry studies is difficult and raises a doubt on the conduct of clinical trials due to lack of trained researchers. The guidelines are prepared keeping in mind the western culture and may not replicate the same results due to cultural variability in non-western countries like India.^[24] The dilemma in obtaining informed consent from subjects with cognitive impairment includes validity of informed consent by subject, implications and validity of third party consent, protection of human subjects. Regulations don't provide information and guidance on ethical issues of psychiatry research.^[25]

CONCLUSION

Though enveloped by challenges, informed consent is an important tool in clinical trials, which facilitates the entry of new therapeutic interventions into the market. No research activity involving human subjects can be conducted and proceed unless informed consent is completely sought. The responsibility of conducting trial ethically and genuinely lies in the hands of those involved in it. Everyone must understand their obligations and should not misuse their power for own benefit. Rights, safety and well-being of trial subjects should always prevail over the interest of science and society, so that a layman never feels being deceived off in name of a social cause. The issue of informed consent in India is a challenge on the part of investigator as a lot of complexities arise. Further, regulations are based on the western guidelines, which do not necessarily reflect the requirements of India. The guidelines on informed consent in India should be based on complex factors such as culture, level of education, demographics and risks involved during the study.

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