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Informed consent in clinical research: Revisiting few concepts and areas

INFORMED CONSENT IN CLINICAL RESEARCH

In the last five-six decades recognition of the moral right of research subjects to make their own choice or to self-determine or decide on the research participation has been one of the most important developments in the field of ethics related to biomedical research involving human subjects. Regulations and guidelines governing the conduct of clinical research require informed consent essentially to be obtained from each human subject prior to research initiation, and all researchers are bound to follow these regulations. Also, prior to conduct of clinical research, it is essential to get the research reviewed and approved from a competent and appropriately constituted institutional review board (IRB) or independent ethics committee (IEC). It is the responsibility of the IRBs/IECs to review a research proposal and ensure that adequate informed consent procedures are determined to be implemented in an ethical way without jeopardizing the rights, safety, and well-being of the human subjects.^[1-4]

Informed consent is one of the most important aspects of research ethics. Regulations requiring informed consent have been promulgated to protect the human subjects participating in clinical research. Basic ethical principle behind informed consent legalities is to protect the

autonomy of human subjects which states that welfare and interests of a subject participating into clinical research are always above the society's interests and welfare. Medical research directed towards treatment advances for society's benefit and betterment can never be built on sacrificing the rights and health of research participants.

ELEMENTS OF INFORMED CONSENT

An informed consent resides on its three critical and essential elements including voluntarism, information disclosure, and decision-making capacity. For an ethically valid and real informed consent, these critical elements are required to be essentially employed and adequately present while informed consent is expressly sought from a research subject.^[5-9]

Voluntarism

Despite being elaborated in various codes of biomedical ethics and regulations, the concept and importance of voluntarism in clinical research has not been realized and practiced much, which otherwise help fulfilling the principle of respect for person. Voluntarism is defined as *the ability of an individual to judge, freely, independently, and in the absence of coercion, what is good, right, and best subjected to his/her own situation, values, and prior history.*^[10] For an ethical and valid consent, the subject's decision has to be a voluntary one. Voluntarism of an individual may be affected by various factors such as intellectual and emotional maturity to make complex decision; illness-related considerations such as psychological effects of dreaded or incurable diseases or severe mental disorders; religious and cultural values and beliefs such as catholic beliefs regarding moral action at the beginning and end of life; relationship with caregiver

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including economic and care burden; and undue influence or coercion for research participation.^[10,11] Voluntarism of vulnerable subjects is usually compromised; therefore, while inviting such patients for research participation and obtaining their consent, special precautions are required to be implemented and mode of consent must be approved by a competent IRB/IEC.

Information disclosure

Information disclosure refers to providing information that is necessary for a patient to make an informed decision and is one of the essential elements of a valid informed consent. For a valid consent, information provided to a research subject should include, but not limited to, health condition for which the research is proposed; nature and purpose/reason of the study; study treatment or intervention and experimental procedures; probable risks and benefits associated with research participation; nature of illness and possible outcome if the condition is left untreated; availability, risks and benefits of alternative treatments; right to withdraw at any time; and any other information seems necessary for an informed decision to be taken by the patient.^[1-4] The forgoing information disclosure is aimed at enabling the patients to make an informed, rational, and logical decision in the light of their cultural, psychological, and social values and beliefs.

The process of information disclosure appears fairly straightforward; however, in real situation it may present difficulties. How much or up to what extent the information should be provided on various aspects of research, such as risks and benefits associated with study intervention, is not clear and is rather a subjective approach depending on the investigator. For example, recounting or repetition of possible adverse effects of a study treatment may make that treatment ill-advised when the treatment is not that risky. On the contrary, if a lately appearing adverse effect is not disclosed to the patient, it raises question on the validity of the consent as the information was not provided adequately. Therefore, researchers are recommended to provide the study-related information adequately, judiciously, and truly maintaining an ethical balance between expected risks and benefits of the intervention under investigation.^[12] Physicians may also elaborate on clinical significance or acceptance of the potential adverse effects in the light of disease severity. For example, fever as an adverse effect for a headache pill is not clinically acceptable; whereas, neutropenia being an adverse effect of an anticancer drug may be clinically acceptable. Furthermore, biased presentation of the information with deliberate intentions of getting the participant to decide according to the wish of researcher would invalidate the consent. Therefore, information disclosure should strictly be free from coercion, fraud, and any biased presentation.

As much information as possible and as patient could assimilate should be disclosed even in cases of emergency and incompetent patients. Investigators are required to involve in the process and to closely monitor the process if delegated to other person. In addition, it is recommended to write a contemporary note in patient's chart expressing the occurrence of informed consent discussion and obtaining the consent.

Decision-making capacity

Decision-making capacity of an individual is defined as *"the ability to understand and appreciate the nature and consequences of health decisions and to formulate and communicate decisions concerning health care"*.^[13] Decisional capacity of an individual depends on his/her cognitive abilities and voluntarism and is adversely affected by cognitive impairment or compromised voluntarism. Decisional capacity comprises of four elements or abilities of (a) understanding the information; (b) appreciation of the situation; (c) rational manipulation of the information; and (d) communicating or evidencing a choice.^[13-15]

A capable individual must be able to have a factual understanding of the information provided to him/her; however, there is much less clarity on (a) what degree or extent of understanding is required for being capable, and (b) how much information, as a threshold value, must be understood by the individual to be considered as 'enough' factual understanding. Researchers are advised to ensure that patient has, at least, understood the purpose of research, risks associated with the research intervention, obligations and consequences of research participation, and his/her right of withdrawing consent any time during the study. For a subject to be considered being capable of making healthcare decision, he/she must be able to appreciate his/her situation realistically. The subject must be able to appreciate his/her health condition, consequences if left untreated, that the purpose of study is research and not the treatment, and consequences of participation in research study. A schizophrenic patient, for example, may not believe that he is ill and may not appreciate that why he is invited to participate in a research. To demonstrate decision-making capacity, subjects should be able to rationally interpret or manipulate the provided or disclosed information for making a rational or logical reason to base their decision or choice upon. Finally, subjects must be able to communicate a reasoned choice or decision taken voluntarily. The choice or decision need not necessarily be communicated verbally, but subjects must be able to express or communicate their choice and preference in some way. Another critical aspect related to choice communication is that the made choice should be sustained over a reasonable time period; however, the patient retains the right of withdrawing the consent any

time. Inconsistency or fluctuation of choice over time might reflect impaired decision-making.

Competency or competence, a related notion, should not be confused with decisional capacity; however both describe individual's ability to make decision. Competency is individual's legal standing to make healthcare decisions or it is a legal determination made by a court of law. For example, a 16-year-old patient may possess the capacity of making decision for him- or herself, but may remain incompetent from legal point of view.^[6,13,16]

OBTAINING INFORMED CONSENT

Obtaining informed consent in clinical research has always been among most sensitive and complex ethical issues. Commonly it is understood that the researcher provides study-related information to the potential participants, and seeks their consent on research participation; however, this is not so always. While conducting clinical trials, depending on patients' abilities and capabilities, various circumstances and situations could practically be encountered that have to be dealt with special precautions and procedures while obtaining informed consent from study subjects. Regulations and guidelines governing clinical research have provided guidance on how and in what manner the informed consent has

to be obtained from study subjects in those various situations^[11,17] [Figure 1].

Competent subjects who can comprehend the research-related information should personally decide and provide the consent on research participation. Conditions posing practical challenges where the informed consent cannot be obtained from the real subject may include situations of medical emergency or obtaining consent from the incompetent subjects. Incompetent subjects (such as minors or patients with severe mental disorders compromising their mental ability to provide the consent etc.) can only be included in a research with the consent of their legally acceptable representative (LAR), preferably guardians. In such situations, there is growing need of customized informed consent procedure tailored to the abilities and understanding of the subject. Subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should also provide the written consent personally and can only be enrolled along with the consent of their LAR. Appropriate approaches can be adopted such as, using simplified easy-to-understand language, information disclosure in small consecutive information pieces focusing on important information, providing repeated information in small units, and providing enough opportunity to ask questions and clarify the doubts. In conditions involving

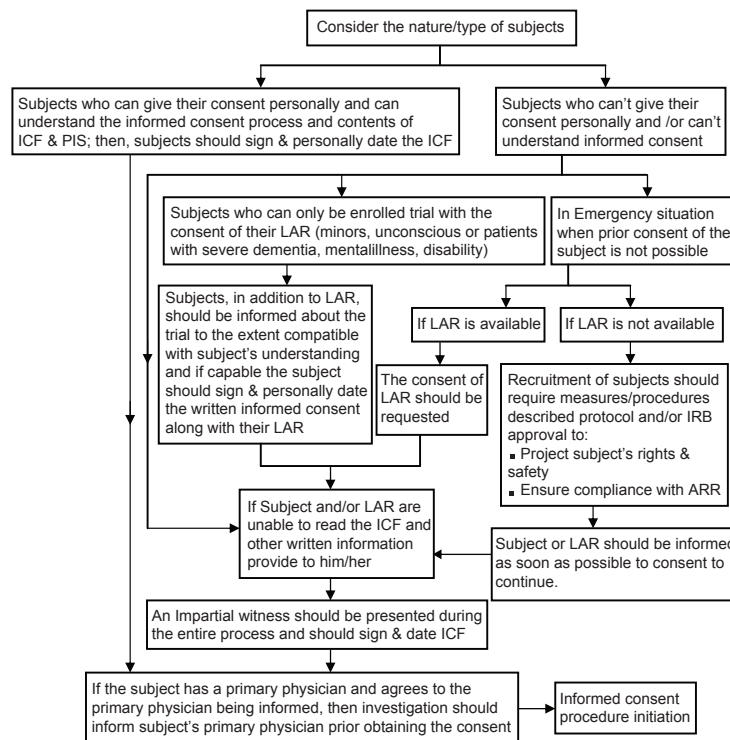


Figure 1: Considerations for obtaining informed consent. ICF, Informed consent form; PIS, Patient information sheet; LAR, Legally acceptable representative; IRB, Institutional review board; ARR, Applicable regulatory requirements

LAR's consent, the potential subject should be informed regarding LAR's consent and subject's any objection should be heeded.^[18,19] Issues related with emergency research are described elsewhere in this article. Ethical complexity associated with proxy and surrogate consent is of special importance for research involving patients with mental disorders.^[20,21]

Furthermore, if a subject and/or subject's LAR are unable to read the written information, an impartial witness should be presented during the entire informed consent discussion. Also, if the subject has a primary physician and wants primary physician to be informed of his/her research participation, then the investigator should inform subject's primary physician prior to obtaining the consent.

While inviting subjects for research participation and obtaining their consent, potential subjects usually receive a document, informed consent document (ICD), comprising of patient information sheet (PIS) containing clinical trial-related all essential information, in easily understandable language, to be revealed to the subjects and a format, informed consent form (ICF), to be signed by the subject and/or subject's LAR confirming their decision of being informed and subject's voluntary participation in the study. Research community has acknowledged the fact that providing a document with all necessary information alone may not fully ensure that the subject has fully understood and comprehended the information required to make an informed decision. Therefore, the investigator needs to ensure that the subject has understood what the participation means to him/her to make an informed decision. This is usually done with an interactive session with the subject interested in participation. This is the point where informed consent procedure (ICP) actually begins and the ICD is primarily designed to evident and help initiate the ICP^[1,17] [Figure 2]. The investigator reviews entire information with the subject and provides him/her ample time to read and comprehend the research-related information, inquire about any aspect of the research, and decide voluntarily on research participation. All doubts and queries of the subject are then answered satisfactorily by the investigator. After comprehending the study information and appraising the results of study participation, subject decides whether to participate in the trial or not. If agreed, the subject provides his/her consent on study participation in written by signing the ICF confirming his/her decision of being informed and voluntary participation in the study.

INFORMED CONSENT: AN ONGOING PROCESS

When a subject has given the consent to research participation, the process of informed consent does

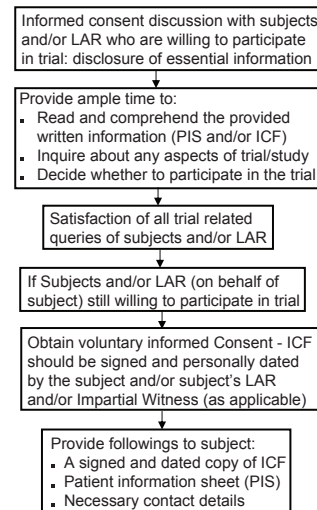


Figure 2: Informed consent procedure. LAR, Legally acceptable representative; ICF, Informed consent form; PIS, Patient information sheet

not end here and obtaining informed consent in clinical research, rather than one-time event, is in fact a dynamic and ongoing process. Also, providing consent does not obligate the study subjects to stay in the research till its completion. Study participants always have the right to withdraw their consent at any time during the study. Continued consent refers to obtaining the consent repeatedly from the subjects, whenever required or indicated during the course of conduct of the study, even if the initial consent was obtained at the study entry. Once the informed consent is obtained from a study subject, obtaining re-consent of the subject is further an important ethical aspect in clinical research in terms of “when re-consent should be obtained”. Even after obtaining informed consent from the study subjects, certain situations may be encountered requiring informed consent again to be obtained.

The researchers are responsible to provide the study subjects, on an ongoing basis, with any new information that has become known during the conduct of the study. If the researcher, during the research, becomes aware of a new information related to study intervention or patients' health condition that may (1) be relevant to the subject's willingness to continue participation in trial; and/or (2) affect adversely rights, safety, and well-being of study subjects; and/or (3) have an impact on study conduct, methodology, procedures, and outcomes; and/or (4) alter the ethics committee approval for the study conduct, the researcher then bears the responsibility to continuously update the study subjects regarding the new information and subjects have right to raise their concerns, ask questions or even withdraw the consent given previously. In such situations, informed consent has to be obtained repeatedly on a continuous basis as and when relevant new information becomes known.^[1,2,22]

Apart from researcher's awareness of relevant new information, there could also be other circumstances requiring informed consent again to be obtained from a study subject who has already given the consent.^[17] Such situations may arise when some serious error has occurred while obtaining informed consent and one or more of essential elements of a valid consent seem to be compromised because of that error. These circumstances are more likely associated with clinical trials of new medical interventions which are highly regulated and where tolerance for such consent errors is critically low, as it may jeopardize the rights, safety, and well-being of potential study subject. The key to identify such situations is to evaluate whether or not the consent error has any possible adverse effect on any of the essential elements of a valid consent, i.e. voluntarism, information disclosure, and capacity, which in turn affects the autonomy of the subject invalidating the consent. Examples of certain possible consent errors may include situations like when obsolete/wrong/unapproved version of ICD, containing inadequate information, was used; language used in ICD is not understandable for the subjects; subject was evidentiary and unduly influenced or coerced for study participation; or LAR and/or impartial witness were not present during the informed consent process whereas it was required.

In addition to the forgoing issues, the aspect of continued consent has got special relevance in connection with clinical research involving patients with mental disorders because such patients who were initially not capable of providing the consent may gain the capacity, during the study, to provide the consent due to study treatment, especially in long-term studies. Gupta *et al.*,^[20,21] has provided a comprehensive review and guidance on various ethical issues and recommendations related to informed consent in psychiatry clinical research.

EXCEPTIONS TO INFORMED CONSENT

As a rule of thumb, informed consent has to be obtained from each study subject, prior to their participation in the research. However, there are certain situations, such as emergency research and therapeutic privilege, which are exceptions to this general rule wherein information disclosure to the subject may be shortened appropriately in part or full. It is noteworthy that in these conditions patients still retain the right to refuse to participate in the research.

Emergency research

Medical emergency refers to circumstances where a patient is in life-threatening situation requiring urgent medical treatment, and where time required for information

disclosure may cause a potential harm to the patient. Such medical situations may be excused of obtaining patient's consent prior medical intervention stating that any treatment delay may put patient's life in danger.^[23] This window of consent exception applies to a limited class of researches involving human subjects who are in need of emergency medical care or intervention, but are not able to give their consent because of their underlying life-threatening medical condition, and who do not have their LAR to represent them.^[24] If subject's LAR is available, the consent of LAR should be requested. In emergency situation, when alternative mechanisms for obtaining consent are not available, information may be disclosed, if possible, in smaller relevant amount to obtain consent without making delay and the subject or subject's LAR should be informed as soon as possible to consent to continue the research participation.^[1,17]

A research study intended to be conducted in such patient population, requiring emergency treatment, is referred to as emergency research. In such emergency research studies, regulations have also provided a narrow exception to the informed consent requirement. The United States Food and Drug Administration (US FDA) has released a detailed guidance on emergency research focusing at informed consent.^[25] According to this guidance, all of the following conditions must be present for a study to qualify to be conducted as emergency research.

1. The human subjects are in a life-threatening situation that necessitates urgent intervention;
2. Available treatments are unproven or unsatisfactory;
3. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention;
4. Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition;
5. The intervention must be administered before consent can be obtained from the subject's legally authorized representative;
6. There is no reasonable way to identify prospectively individuals likely to become eligible for participation;
7. Participation in the research holds out the prospect of direct benefit to the subjects; and
8. The clinical investigation could not practicably be carried out without the waiver.

Emergency research involves the most vulnerable subject population, i.e. subjects with no capacity to control what happens to them and no capacity to consent, in a setting where the emergency circumstances require prompt action, and generally provide insufficient time and opportunity to

locate and obtain consent from subject's LAR. Recognizing the lack of autonomy and subjects' inability to provide informed consent, additional protective measures are required for involving human subjects in emergency research. To protect these vulnerable subjects, regulations put additional responsibilities on parties involved with such research including sponsors, clinical investigators, and IRBs. These additional responsibilities include consultation with representatives of the community(ies) in which the research will take place and from which the subjects will be drawn; public disclosure of information before the start of the study and following its completion; a commitment by the investigator to try to locate the subject's LAR or contact a family member to determine whether the family member objects to the subject's participation; and establishment of an independent data monitoring committee by the sponsor.^[24,25]

Therapeutic privilege

Therapeutic privilege refers to a situation or practice whereby an investigator or a physician may not reveal, usually a part of, medical information to a patient related to diagnosis or treatment of the disease condition when they believe that disclosure of such information would cause a potential harm to physical, mental, or social well-being of the patient, and the harm is as serious as is medically contraindicated.

Therapeutic privilege is distinct from situations where information disclosure is excused based on the non-feasibility of information disclosure such as emergency situations; however, is also an exception to the ethics or general rule of obtaining informed consent. Therapeutic privilege, however, should only be exercised by the researchers or physicians when a serious harm to the patient well-being, such as prompting suicidal wish or behavior, is strongly believed and can be demonstrated (e.g. from their expertise, experience, or some other means). This exception to the informed consent does not apply to the situations whereby information disclosure will merely lead to refusal of medical care or non-acceptance to participation in a research study that the physician or researcher thinks beneficial.^[26-28]

Therapeutic privilege, however, is more likely observed in routine medical care as compared to research settings where blunt, but true, disclosure of a harsh reality would further aggravate patient's distress diminishing his/her autonomy, and making him/her incapable of participating in treatment-related decision-making. For example, disclosure of a newly diagnosed incurable malignancy may lead to profound mental and emotional reactions in a patient already suffering from a serious illness. In such situations, withholding or modification

of information, deemed essential otherwise, may be considered as an ethical imperative on the grounds of therapeutic privilege.^[12]

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