Informed Consent: A Real Challenge in Clinical Trials

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Abstract
Informed consent is an agreement to do something or to allow something to happen only after all the relevant facts are known. It has a long history starting from early 1947 to till now with recent amendments. Informed consent play a major role in the clinical trials and is crucial factor on which the success of any clinical trials is dependent. It is classified in several types like parental consent, Assent, Verbal and short form among which to get a informed consent in assent type is a real challenge. Assent is a child’s (7-17yrs of age) affirmative agreement to participate in research and must be written at the appropriate reading level of the youngest subject in the age range using simplest terminologies. This review article discusses about the basic elements of informed consent and the process to be followed while obtaining informed consent.

Key words: Informed consent, Agreement, Assent, Documentation, Clinical trials.

INTRODUCTION

Informed consent is an agreement to do something or to allow something to happen only after all the relevant facts are known. In contracts, an agreement may be reached only if there has been full disclosure by both parties of everything each party knows which is significant to the agreement. A patient’s consent to a medical procedure must be based on his/her having been told all the possible consequences, except in emergency cases when such consent cannot be obtained. A physician or dentist who does not tell all the possible bad news as well as the good, operates at his/her peril of a lawsuit if anything goes wrong. In criminal law, a person accused or even suspected of a crime cannot give up his/her legal rights such as remaining silent or having an attorney, unless he/she has been fully informed of his/her rights.[1]

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

The Nuremberg Code 1947
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

Declaration of Helsinki 1964
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.

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The Belmon Report 1979

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.

CIOMS Guidelines 1982

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.

International Conference on Harmonisation GCP 1996

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 well-being 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.

Classification of Consent

1. 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.
2. 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.
3. Assent: Assent is a child’s affirmative agreement to participate in research. If the subject is 7 to 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.
4. Verbal: Verbal consent still contains all elements of written consent; however, the participant is verbally read the elements and verbally agrees to participate.
5. 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.

The Process

Informed consent is a process that begins with the recruitment and screening of subjects and continues throughout the subject’s involvement in the research. It includes: Providing specific information about the study to subjects in a manner comprehensible to them. Answering questions to better ensure subjects understand the research and their role in it. Giving subjects adequate time to consider their decisions. Obtaining the voluntary agreement of subjects to participate in the study. The agreement is only to enter the study, as subjects may withdraw at any time, or decline to answer specific questions or complete specific tasks.

Documentation

Documentation of consent provides a record that the initial process took place. It generally consists of a consent form signed by the subject or the subject’s legal representative. In practice, this document is often used as a tool for engaging in the consent process, which consists of providing information about the research to potential subjects. Sometimes, informed consent can be documented by other means, as approved by an Institutional Review Board (IRB), for example, audio or video recording.

Information That Must Be Provided To Subjects

The federal regulations about informed consent list specific elements of information that must be provided to subjects. The elements are divided into two categories. One category includes basic elements to be provided to subjects. The second category lists elements that are included if appropriate. The two lists are provided below with comments.

A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures that are experimental.

- A description of any foreseeable risks or discomforts to the subject.
• A description of the benefits to the subject or to others.
• A disclosure of any alternative procedures or treatments that may be advantageous to the subject.
• An explanation of how the institution/investigator will maintain confidentiality of records.
• For research involving more than minimal risk, an explanation regarding whether medical treatment is available if injury occurs.
• Contacts for further information about the research study and about the rights of research subjects. If research-related injury is possible, subjects must be told whom to contact should injury occur.
• A statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that the subject may discontinue at any time.
• All consent forms must state explicitly that subjects may withdraw at any time and may choose not to answer questions or complete specific tasks. In keeping with this requirement, Web-based surveys must be designed so that subjects are not forced to respond to a question before moving to the next one.[8]

The Steps for Obtaining Informed Consent:
I. Awareness of, and consultation with, national and/or regional health research bodies
• Be aware of existing national and/or regional health research guidelines which may set out specific expectations to protect the interests and well-being of participants, their communities and the national health research system.
• Consult national and/or regional research institutions on any proposed human subject research which will take place within their boundaries.
• Where appropriate, consult with the local leadership or, when the research involves vulnerable populations, with the organizations representing or working in the interests of potential participants.

II. Discussions with community leadership:
• Obtaining the agreement of local community leadership for the proposed research is almost always good research practice and is mandatory in some communities.
• Agreement from the community leadership is obtained prior to, but does not replace, the consent and/or assent of individual participants.
• Community consent is generally obtained through a process of dialogue with the community leadership and often does not require written agreement.
• There are, however, some countries and communities which require written evidence of consent and of the nature of any collaboration between the community and the proposed research. It is the researchers’ responsibility to become aware of, and respect, these requirements.
• While support from the community leadership can lead to research practices which are collaborative, culturally-sensitive and which facilitate a more supportive research environment, researchers should be aware that what constitutes community leadership is not always clear, nor always ethically supportable, and that consultation does not necessarily result in agreement.

III. Recruiting and informing research participants:
• Researchers may meet individually or in small groups with potential participants in order to recruit and inform them of the research.
• Sometimes, however, broader and more open approaches, such as information posters, brochures, announcements and community meetings may be better ways of introducing community members to the research which they are being invited to participate in.
• In all situations, the information that is shared with the community and potential participants must be provided in a manner that is understandable to participants and which, therefore, allows them to make an informed decision.

IV. Knowing and respecting community practices:
• The degree of autonomy that individuals have to make decisions about their lives, including whether or not to agree to be a participant in a research study, varies among cultures.
• In some cultures, it is the norm for the head of a household to either make all such decisions or to lead the group towards a decision. A husband, father or brother may traditionally have the responsibility for decisions involving a wife, mother or a daughter of any age.
• In seeking informed consent, the researcher must consider these norms and traditions while still seeking the individual informed consent of the potential research participant.
• The research participant must give her or his own consent to participate even when consultations with other family or community members has occurred.
• In all situations, researchers should be prepared to recognize unspoken reluctance on the part of potential participants and to respect their wishes.

V. Accepting oral consent
• Oral consent is acceptable from research participants who are illiterate and, therefore, cannot read or sign informed consent forms.
• However, the informed consent process requires that researchers ensure firstly, that the information they provide about the research is in an understandable form and, secondly, that a literate witness is available to sign on behalf of the participant after the participant has given oral consent.

• Oral consent may also be audio-recorded and this recording witnessed as further confirmation.

• In addition to the signature of a literate witness, agreement of participants who are illiterate should be indicated by including his/her thumb print on the ICF.

• Researchers should do their best to ensure that witnesses are not part of the research team. Whenever possible, participants should choose their own witness.

• There are very few situations other than illiteracy in which oral consent is acceptable and these always necessitate prior approval from an IRB and/or the ERC. It is, for example, possible that written consent may be waived if there is a possibility of unsupportable danger to the participant as a result of signing or when there is minimal risk coupled with anonymity. However, the vast majority of research requires written consent either of the participant or, in the case of illiteracy, of a literate witness.

VI. Obtaining consent and assent in research involving children

• Before seeking consent and assent to involve children in research, it must be demonstrated that comparable research cannot be done with adults to the same effect and scientific impact.

• Once it has been determined that the research should be permissible, researchers must obtain parental/guardian consent on an ICF for all children.

• WHO supported research follows the Convention on the Rights of the Child where child means ‘every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier.’

• Children sufficiently able to understand the proposed research should have the opportunity to be informed about the research, to have their questions and concerns addressed and to express their agreement or lack of agreement to participate.

• While the age at which this informed assent should be taken varies, researchers should consider asking for assent from children over the age of seven years with assent taken from all children over the age of twelve years.

• Children express their agreement to participate on an informed assent form (IAF) written in age appropriate language. This form is in addition to, and does not replace, parental consent on an ICF.

• Assent which is denied by a child should be taken very seriously

VII. Obtaining consent from vulnerable populations

• When seeking consent from participants in vulnerable populations, researchers should ensure that the participants will not be exploited, including being placed in situations which compromise their safety or dignity and which place them in a position of even greater powerlessness.

• Researchers may need to make extra allowance to ensure that the consent is genuine and does not place added risk or stress on the participant.

• As with all WHO supported research, participants may be reimbursed for expenses incurred as a result of the research and compensated for time lost from work. WHO does not support inducements to participate.[9]

Challenges and Practicalities Of Obtaining Parental Consent And Child Assent In Paediatric Trials

Obtaining Informed Consent from Parents/Legal Guardians

Recruitment of paediatric patients into clinical studies is challenging for several reasons. These include parental anxiety relating to the diagnosed condition and prognosis, and to submitting their child to ‘experimental procedures’. The fear of invasiveness and pain for their child, and taking responsibility to consent their child to a study, can greatly concern parents and result in their not giving consent. This is particularly important for studies in newborns and infants where the child cannot express any willingness to participate. The structure and content of the parent information sheet and the parent informed consent form follows the same international rules as for an adult patient information sheet and informed consent form. In general, both parents need to give consent and sign the informed consent form, although there are regions where the consent of only one parent is considered adequate.[10]

Informed consent should be obtained from parents in accordance with local laws and regulations. Important elements to be considered when obtaining parental consent are:
General

- Complete and balanced information
- Understandable information Thorough risk and benefit assessment
- Measures taken to preserve child’s safety
- Rights of parents and child
- Consider child’s presumed will
- Voluntariness of participation
- Enough time for parents to consider the options available and discuss with family
- Investigator and site staff available to answer questions
- Keep parents informed throughout the study

Parent information package

- The need and purpose for clinical studies
- Rationale for experimental treatment
- Background information on the disease
- Detailed information on the study drug
- Condition under study

Trust and a close relationship between site staff, the parents and the child are of crucial importance and have been shown to be one of the major factors for parents agreeing to a clinical study in addition to balancing risks and benefits to their child. Besides that, altruistic factors, like helping to develop medical knowledge and learning more about the child’s disease, play an important role in parental decision making.\[11,12\]

Obtaining Assent from Paediatric Subjects

In paediatric study settings a triad exists between the investigator, parents and child, which requires special attention in the informed consent process.\[13\] The child should be included in the decision-making process to the extent possible depending on their age and maturity. According to the Declaration of Human Rights, a child is to be considered as a person with all basic human rights from the day of birth. Asking the child for assent recognises the dignity, integrity and autonomy of self determination and respects the expression of the child’s willingness to participate. Assent means having the child express agreement to undergo a medical procedure in a clinical trial. The informed consent process should be conducted appropriately to discover the will of the child and respect the decision-making capability of the child. It is necessary for site study personnel to have experience in the caring for and treatment of children in the respective age group, and that they are familiar with age-specific issues. The parents must assist in determining the will of the child which also needs to be considered in the parental consent. Generally, depending on the age range of clinical study participants, separate information sheets and assent forms should be created to provide information in age appropriate language and wording and should be focused on the purpose of the trial, the procedures required, the benefits and risks, the voluntarily participation in the trial and most importantly the child’s agreement to participate. The child’s involvement in the decision process and ability to give assent increases with their age; in the US, the age of assent is endorsed to be seven years, whereas in the EU, with no clear guidance, nine years is considered reasonable,\[14,15,16\] Of course there is variation among children of the same chronological age in the level of understanding, mental maturation and ability to make decisions. The underlying condition and disease pattern also plays a role. The information provided to the child should be adequate to his/her individual level of understanding but also consider the child’s individual psychological and intellectual maturity and social environment. Children are not autonomous individuals and therefore decision-making is also dependent on the social structure of the family. Some children of the same age may be fully involved in the consenting process and be able to give informed assent, whereas others will feel more comfortable deferring the decision to their parents. The investigator must decide whether an individual child has the ability to understand the information and provide assent. The minimum age of assent should be decided in advance of study start with the Ethics Committees, considering the study setting and underlying disease.\[10\]

Paediatric participants of appropriate intellectual maturity should personally sign and date a written assent form. In all cases, the paediatric participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. There might be clinical study settings, however, where the child’s dissent may be overridden when participation is likely to benefit the child (e.g., life threatening diseases or if no alternative therapies exist or these are only available in the context of research).\[14\]

CONCLUSION

Informed consent is an important key in clinical trials, which enhances the commercialization of new therapeutic interventions. Research studies including human subjects can be conducted and preceded only if informed consent is completely sought. The responsibility of smooth and effective conductance of trial ethically and genuinely lies in the hands of those involved in it. Rights, safety and well being of trial subjects should always prevail, so
that a nonprofessional should never have a feeling of being deceived in the 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. Carefully planned design, implementation, and follow-through of sound recruitment and enrolment strategies contribute to the efficiency and success of clinical research trials from initiation to study close-out. The guidelines on informed consent in India should comprise of important factors such as culture, level of education, demographics and risks involved during the study.

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