

Informed consent in biomedical research – A review of its importance and current global guidelines

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ABSTRACT:

INTRODUCTION: Informed consent is an essential step in the ethical conduct and regulation of research, and it has been a keystone in preparing guidelines for conducting research and ethical oversight of research. It is the process by which a patient/participant consents to participate in a research project after obtaining detailed information about the likely procedures, risks, and benefits.

OBJECTIVES: The article aims to trace the evolution of guidelines for obtaining informed consent, knowledge of which is required in the conduct of biomedical and health sciences research by researchers with varied background and experiences. It also highlights the challenges in obtaining a valid informed consent.

MATERIALS AND METHODS: The following electronic databases were searched through October 15,2017: 1) PubMed/MEDLINE; 2) Cochrane Database of Systematic Reviews; 3) Science Direct; and 4) ISI Web of Science. Two separate searches were performed. The first search used the following search parameters ([MeSH terms] Informed consent AND [MeSH terms] (Codes of ethics OR Bioethical issues) AND [MeSH terms] (Challenges), and the second Used ([MeSH terms] Informed consent AND [MeSH terms] (Ethical committees).

RESULTS: Articles were initially screened based on the titles and abstracts. The accepted articles were reviewed for study design. All references cited in the accepted articles were reviewed to identify additional papers not identified in the database searches. Disagreement regarding inclusion or exclusion of the retrieved papers was resolved by discussion, producing the final set of articles used in this review.

CONCLUSION: Informed consent is much more than a signed form. In spite of obtaining informed individual consent, it is most likely that the participants/ patients may not be fully aware of their rights and in this regard, the role of investigator is crucial.

KEYWORDS: Informed Consent, Research, Biomedical, Guidelines

Introduction

Informed consent is an essential step in the ethical conduct and regulation of research, and it has been a keystone in preparing guidelines for conducting research and ethical oversight of research. It is the process by which a patient/participant consents to participate in a research project after being informed of its procedures, risks, and benefits (1). There are many ethical issues that are embroiled with the informed consent process. Essentially, informed

consent consists of three steps - firstly, the research team provides full and transparent information about the nature of the project; secondly, the participant must understand what is being asked and should be competent to decide; thirdly, the person must decide freely whether to participate or not to participate (2) (Fig-1).

This review aims to trace the evolution of guidelines for obtaining informed consent - knowledge of which is required in the ethical conduct of biomedical and health sciences research by researchers with varied background and experience. The following electronic databases were searched through October 15,2017: 1) PubMed/ MEDLINE; 2) Cochrane Database of

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Study Selection Criteria: Articles were initially screened based on the titles and abstracts. The accepted articles were then reviewed for their study design. All references cited in the accepted articles were reviewed to identify additional papers not picked up earlier in the database searches. Disagreement regarding inclusion or exclusion of the retrieved papers was resolved by discussion among authors thus producing the final set of articles used in this review.

1. The evolution of informed consent The basic principles of ethics in medical practice emanate from the Hippocratic code of conduct which specifies that the physician will use the treatment to help the sick according to his ability and judgment, but never with a view to injury and wrong doing. Claude Bernard extended it to the domain of research, saying that one should not injure one person regardless of the benefits that might come to others (3). The events that led to the implementation of the principles behind the informed consent process in scientific research were some of the most horrific in human history involving atrocities committed on prisoners by Nazi scientists which paved the way for creation of the Nuremberg Code. This Code states that all those who are participating in an experiment are required to give voluntary consent free of undue influence such as “coercion, fraud, duress, or deceit” (4). However, this Code did not establish a method that would ensure that the rules were complied by the physicians/scientists conducting research. The infamous Tuskegee syphilis study in USA (5) and the landmark publication by Beecher on the irregularities that occurred in at least 22 medical research projects in United States changed all this (6).

Ever since then, the scientific community has continued

to revise such principles in order to ensure the ethical treatment of participants. The Declaration of Helsinki and the Belmont Report also indicate the ongoing need to refine the rules and regulations behind the informed consent process. The Belmont Report identified three basic principles which are to be followed by all researchers-these include respect for person, beneficence, justice. Among these, the ethical principle of respect for persons is the most important principle with regards to the informed consent process which establishes that all human participants are to “be treated as independent and autonomous individuals capable of self-determination.” This implies that all participants must provide informed consent to be involved in a research project, they must be provided with adequate information about the project, they must understand the research protocol, and they must be able to withdraw from the project at any point. In recent years, widespread debates surrounding trials of antiretroviral drugs in Africa have led to the reconsideration of several aspects of internationally sponsored research (7, 8). The Declaration of Helsinki, issued by the World Medical Association in 1964 is a landmark document in the field of ethics in biomedical research and has guided the development of international, regional and national legislation and codes of conduct since then. The Declaration, amended several times, most recently in 2013, is a comprehensive international statement of the ethics of research involving human subjects. It regulates ethical guidelines for physicians engaged in both clinical and non clinical biomedical research. The Helsinki Declaration (2000) on Informed Consent declared that 'in any research on human beings, each potential subject must be adequately informed of the aims and objectives, methods, sources of funding, any possible conflict of interest, the researcher's institutional affiliations, the anticipated benefits and potential benefits and potential risks of research and the potential discomforts it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw at any time without reprisal' (9).

2. Obstacles to Informed Consent

2.1. Language Barrier: Web page related to the Federal regulation 45CFR46.116 of the United States Department of Health and Human Services states that informed consent has to be obtained in a language that is understood by the participant or their representative, but misunderstandings can still occur because of inadequate language translations. The quality of the translation is almost as important as the informed consent itself. Research has shown that the use of untrained translators in clinical settings tend to make frequent errors that in some cases result in dangerous misinterpretations. Another problem with the use of untrained translators such as auxiliary staff in the hospital is that it can result in violation of patient confidentiality which can strain the participant-researcher relationship. Research has also shown that words or phrases translated from English to another language can result in drastic and erroneous change of meaning (10). Untrained translators will not realize how words that are spelt almost the same in other languages do not necessarily have the same meaning as they do in English.

2.2. Comprehension and capacity: Although language is an issue in securing informed consent, obstacles to comprehension go beyond the linguistic barriers. In some cultural groups there may be little or no understanding of bio-medicine and researchers lacking knowledge of traditional belief systems may be wrong to conclude that the individual lacks capacity.

2.3. Literacy: Dine and Bhui (11) addressed the dilemmas of conducting research among individuals who are unable to read or write even in their own language. Illiteracy however must never be understood to mean that a potential participant is unable to understand the information that is given, but it does mean that the information may need to be presented differently. Moreover, in societies where verbal communication is often relied upon, written contracts may be mistrusted or not upheld and asking for a signature may mean offence.

2.4. Religious and Cultural influence: Researchers

designing informed consent forms must consider the negative effects that participants might experience due to religious beliefs when participating in research projects. Having a full understanding of the methods involved in the experiment will enable a person to adequately judge if they want to participate in the experiment. Researchers must consider how the methodology of the experiment can come into conflict with the rules of behavior set by a participant's religion. For example, the Jehovah Witness religion places strict rules of conduct on its followers when it comes to the type of medical attention they can receive.

2.5. Power relationship: A researcher may be seen as an authority figure and the patient may be afraid that failure to comply will have serious consequences such as refusal to treat. Such extreme differences in knowledge and authority must raise doubts about the validity of consent (12).

3. Understood consent versus informed consent: It is assumed that the individual who signs the consent form does so with full understanding of what is stated on the informed consent document. However, whether the participating subject has truly understood the information given is very difficult to evaluate since there is no established method to measure the level of understanding. Many individuals sign the consent form to participate without being fully aware of what they are signing. A study conducted by Appelbaum *et al* (1987) reports that 'research subjects systematically misrepresent the risk/benefits ratio of participating in research.' They implicated this to failure to understand the research methodology. This study showed that 69% of the participants failed to understand the meaning of randomization (13). Although not conclusive, available data suggests that research participants may frequently not understand disclosed information. For example, approximately 30% of participants in a cross-section of oncology clinical trials believed that their treatment had already been established to be the best treatment for their type of cancer (14). In a randomized trial of β -blocker drugs to prolong the lives of patients with history of myocardial infarction, 44% of research

participants interviewed did not know that they were assigned to treatment or placebo by chance (15). Karim et al evaluated the consent process for HIV testing in an antenatal clinic in South Africa. They found that despite the fact that researchers followed the procedures for obtaining informed consent, 84% of participants believe that it was mandatory to participate (16). Many other studies suggest that similar shortfalls in understanding are widespread (17, 18, 19, 20, 21).

All too often the informed consent process is viewed by members of research teams as a challenge of getting participating subjects to sign on a form. Informed consent is, however, much more than a signed form. Rather, it is a process, often iterative, in which the participating subject is provided sufficient information about a study in order that they can make a truly informed decision about participation. It demands substantial effort from the research team in producing appropriately formatted and readable and most importantly understandable informed consent documents in plain language. Achieving truly understood consent involves the researcher spending significant one-on-one time with the subject, explaining in simple language what is proposed and then using so-called repeat-back techniques to test the understanding of the participants. This is very important if the research involves randomization to different treatments or use of a placebo arm and, in particular if the research involves more than minimal risk.

4. Interventions to improve research participants' understanding of informed consent for participation in research:

Given the importance that informed consent is for both the protection of human rights and the ethical validity of research experiments, it is important and ethical to try to amend the problems caused by the misunderstanding of information. The methods that have been suggested are: 1) conducting a demographic analysis of the geographical location of the research projects. 2) hiring professionals to translate all the information related to the experiment. 3) taking extra time to fully explain the informed consent form. And 4)

administering small quizzes about the information covered in the consent form. Interventions using modern techniques like multimedia technology, detailed enhanced consent forms, and extended discussion with social scientists and educators. These methods have been proposed to improve research participants' understanding of disclosed information and to give genuine consent. Flory and Emanuel (2004) in a systematic review concluded that multimedia and enhanced consent form interventions do not consistently improve research participants' understanding. Person-to-person interactions, more importantly the extended discussion interventions, may be more effective in improving understanding (22). Another method that can be implemented to aid the informed consent process is testing for understanding. A short quiz focusing on the important aspects of the research project such as its methodology, purpose, risks, and benefits after the informed consent form is explained would help researchers identify potential problem areas. Researchers can use the erroneous answers as a guide for conducting further explanation sessions.

5. Global guidelines on informed consent:

5.1. *World Medical Association Helsinki guidelines, 2003:* Helsinki guidelines in their 2003 revision adopted the following guidelines-The physician should obtain the potential participants freely given informed consent, preferably in writing. Even if the consent cannot be obtained in writing, consent must still be formally documented and witnessed. In cases in which the potential participant is legally incompetent, physically, or mentally incapable of giving consent or is legally incompetent minor, the investigator must obtain informed consent from the participant's legally authorized representative in accordance with applicable law.

5.2. *National Bioethics advisory Committee, 2000 (23):* The research group should develop culturally appropriate ways of disclosing the information necessary for adherence to substantive ethical standards of informed consent, giving particular attention to disclosures

relating to diagnosis and possible post trial benefits to the participant. Procedures must be developed and described in such a way to ensure that potential participants understand the information provided in the consent process.

While the permission of a community representative may be sought before researchers approach potential participants, in no case may such permission replace the requirement of obtaining a competent individual's informed consent without coercion or inducement. Researchers working in developing countries should indicate in their research protocol how they will minimize the likelihood that potential participants will mistakenly believe that the research purpose is solely to administer treatment rather than to contribute to scientific knowledge.

5.3. *Nuffield Council on Bioethics, 2002 (24)*: Verbal consent is acceptable only if written consent is inappropriate. The consent of a senior member of the family member or community leader may be required in addition to individual's consent. The council also recommends adopting the concept of 'genuine consent' as opposed to 'informed consent.'

5.4. *Council for International Organizations of Medical Sciences, (CIOMS) 2002 (25)*: In all biomedical research involving humans the investigator must obtain the voluntary informed consent of the potential participant or in the case of an individual who is not capable of giving informed consent, the legally authorized representative in accordance with applicable law. The use of a waiver of informed consent is regarded as uncommon and exceptional and must in all cases be approved by an ethical review committee. Written consent is preferably required when appropriate. Multiple forms of consent are acceptable. In the case of research posing minimal risks, participants may waive consent. The council lists 26 essentials of research that must be addressed during the consent process (Box-1).

5.5. *European Union guidelines, 2001 (26)*: The consent of family or community leader may be required in addition to obtaining an individual's consent. Verbal

consent is appropriate only if the participant is illiterate. These guidelines provide a checklist of eight essential aspects of research that should be addressed during the consent process.

5.6. *ICMR Guidelines regarding the Informed Consent process*: All the research involving human participants should be conducted in accordance with the four basic ethical principles, namely autonomy (respect for person / participant) beneficence, non-maleficence (do no harm) and justice. The guidelines that are framed are directed at the application of these basic principles to research involving human participants. For all biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed Consent Form with Participant/ Patient Information Sheet should have the components as may be applicable as in Box-2 (27).

In the context of developing countries such as India, obtaining informed consent has been considered many times as difficult/ impractical / not meeting the purpose on various grounds such as incompetence to comprehend the meaning or relevance of the consent and culturally being dependent on the decision of the head of the family or village/ community head. In the new 'National Ethical Guidelines for Biomedical and Health Research involving Human Participants'(2017) specialised areas such as informed consent process, biological materials, biobanking and datasets and vulnerability have been expanded into separate sections. Essential and additional elements of the informed consent process are given in Box-3 (28).

5.6. *World Medical Association, Helsinki guidelines (2013)*: Helsinki guidelines in their 2013 revision adopted following guidelines regarding informed consent as in Box-4 (29).

5.7. *Draft guidelines on Audio-visual Recording of Informed consent process in Clinical trials issued by Central drugs standard control organization (CDSCO) and its pros and cons*

CDSCO (Central drugs standard control organization) vide F. No. GCT/20/SC/Clin./2013 DCG1 dated 19.11.2013 has issued direction that in all clinical trials, in addition to the requirement of obtaining written informed consent, audio-visual recording of the informed consent process of each trial subject, including the procedure of providing information to the subject and his/her understanding on such consent is required to be done while adhering to the principles of confidentiality. Such audio-visual recording and related documentation would be preserved. This is applicable to the new subjects being enrolled in all clinical trials including Global Clinical Trials. It is included as draft rule in the gazette of India notification dated 7th June 2013 (30). Details of the draft appear in Box-5.

5.71. *Advantages and disadvantages of the audio-visual recording of the informed consent : have been discussed in depth by Kulkarni et al. (31).* There are many anticipated advantages of AV recording like reliability, transparency, and improvement in quality of conduct of informed consent process. However, at the same time the industry will need to address challenges in infrastructure, maintaining confidentiality, cost implication, and so on.

6. *Assent and Dissent in Paediatric Research:* Children are often proclaimed as being very important members of society because they represent our future. However, it is often unclear how society uses its resources or creates policies to ensure that it invests in children's health. History has shown that children may be exposed to serious unintended harms from medications if adequate research is not performed (32, 33, 34). Most child health care providers must often rely on evidence that has been generated on adult populations though children are not small adults (35) and both the safety and efficacy profiles of medications may be significantly different for children than adults due to differences in developmental physiology, disease patho- physiology, or developmental pharmacokinetics and pharmacodynamics (32, 33, 34, 35, 36).

Guidelines around the world require children to

provide assent for their participation in most research studies. Yet, little further guidance is provided on how review committees should implement this requirement, including which children are capable of providing assent and when the requirement for assent may be waived on the grounds that the research offers participating children the potential for important clinical benefit. This suggests children are capable of assent when they become able to understand the research in question. Investigators and review committees who attempt to implement the assent requirement must determine at what age children become capable of providing assent. Unfortunately, research ethics guidelines provide little guidance in this regard. In USA, US federal regulations specify only that the determination of which children are capable of assent should be based on the children's 'ages, maturity, and psychological state' (Department of Health and Human Services, 11 45 CFR 46.608a). This guidance leaves many questions unanswered. Which aspects of children's age, maturity, and psychological state should investigators take into account when determining whether they are capable of assent? Some commentators defend the age seven threshold by appeal to the centuries old 'Rule of Sevens', which 'has stood at least ever since the time of Edward the Third' (1327-1377) to determine an age threshold for assent (37). Rule of Sevens states, roughly, that children under age seven do not have the capacity necessary to make their own decisions; children from seven to fourteen years of age are presumed not to have this capacity until proven otherwise in individual cases, and children over age 14 are presumed to have capacity to make their own decisions and lead their own lives, unless proven otherwise.

6.1. ICMR GUIDELINES regarding Informed Consent In Paediatric Research:

Before undertaking trial in children, the investigator must ensure that guidelines are followed as in Box-6. In cases of research involving children, a parent or legal guardian of the child should give proxy consent. In case of research on children, the assent of the child should be

obtained to the extent of the child's capabilities such as in the case of mature minors from the age of 7-18 years of age (27).

As per the recent National ethical guidelines for biomedical research involving children, for children between 7 (84 months and above) and 11 years of age, oral assent must be obtained in the presence of parent/LAR (legally authorized representative). For children between 12 and 18 years of age, written assent must be obtained. If a child becomes 13 years old during the course of the study, then written assent must be obtained in addition to parent/LAR consent (38). In most of the cases, children will not know whether research participation will be distressing until they experience it. Hence, requiring children to make a prospective decision whether to enrol does not offer an effective mechanism to protect them from harm, particularly when children may be reluctant to go back on agreements made with doctors. Children also may find it very distressing to be asked to make decisions about research they cannot understand. Thus, protecting children from harm does not seem to support, and may well conflict in certain cases, with the requirement to ask children to decide whether to enrol in non-beneficial research before they are able to understand the research in question. In contrast, once children are enrolled for research, they will be in a very good position to assess whether it is causing them distress. Also, these children who experience distress will communicate this verbally or through body movements, protection of children from harm supports adoption of a dissent requirement to supplement existing assent requirements: the dissent of all children should be respected in the context of research which is not beneficial (39, 40, 41).

7. Challenges of Informed Consent in Cluster Randomized Trials (CRT):

CRTs raise at least 4 concerns for handling participant informed consent (42). First, the hierarchical structure of such trials implies the consideration of 2 levels of consent. The first level is the "guardian," as defined by Edwards *et al* (43) who must agree to participation and

randomization. The other level is participants embedded within clusters.

Second, some interventions (such as fluoridation of water supply or computer-based tools to help physicians while prescribing) apply (or not) to the whole cluster, and individual participants have no opt-out option. Participant consent can therefore cover different things, and thus, Hutton (44) distinguished 3 types of consent: (i) consent that routinely held data on individuals be collected, (ii) consent regarding the collection of supplementary data and (iii) consent for active participation.

Third, randomizing large clusters such as hospitals, villages, or geographical areas implies logistic difficulties that cannot be overcome to obtain individual informed consent. Fourth, full information given to the cluster participant may compromise the internal validity of the trial because of selection bias (lack of allocation concealment induced by a randomization of clusters before recruitment of participants) and group contamination. Blinding participants to the study hypothesis or delivering differential information may then greatly help prevent or reduce bias. These situations led the CIOMS to consider the possibility of a transfer of consent from the individual to the cluster level. The person in charge of the cluster has authority to give permission for the cluster to participate in the study and to be assigned on a random basis to one arm or another of the study, and thus, consent to the study is collective.

Conclusion

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective participating subject or, in the case of a subject who is not capable of giving informed consent, the proxy consent of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be treated as uncommon and exceptional, and must in all cases be approved by an ethical review committee. Valid informed consent is a decision to participate in

research, taken by an individual who is competent to decide, who has received the necessary information; who has adequately understood the information; and who, after understanding the information that is given, has arrived at a decision without having been subjected to duress, undue influence or inducement, or intimidation. This safeguard of interest of the participating subject is particularly important as many individuals are limited in their capacity to give adequate informed consent; they include vulnerable population such as young children, adults with severe mental or behavioral disorders, and persons who are unfamiliar with medical concepts and technology.

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