

*Review Article*

## **Informed Consent for Inclusion into Clinical Trials: A Serious Subject to Note in the Developing World**

Morteza Izadi<sup>1</sup>, Mozghan Fazel<sup>\*2</sup>, Taha Nasiri-Vanashi<sup>3</sup>, Seyed Hasan Saadat<sup>1</sup>, Saeed Taheri<sup>4</sup>

1. Health Research Center; Baqiyatallah University of Medical Science, Tehran, Iran.

2. International Travel Medicine Center of Iran, Tehran, Iran.

3. Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

4. Dr. Taheri Medical Research Group, Tehran, Iran.

### **Abstract**

**Introduction:** Informed consent is a critical issue especially in conducting clinical trials that expose human life to medical or surgical interventions. It necessitates a long and complex process through which the participant is presented with all potential favorable and non-favorable consequences upon getting enrolled in the study.

**Review:** The process of taking informed consent is well-understood in developed countries, with every effort taken to enhance and maintain the autonomy of patients and their right to make an informed choice of whether to participate or not. This may not be the case in the developing world. The information given to patients before the trial might not be properly developed and presented, an issue that can result in serious threat to the decision-making process. On the other hand, investigators should remember that enrolling people into a trial with no potential benefit for themselves cannot be considered ethical. In the current debate, we aim to address the issue of how respectfully and ethically clinical research trials can be done on human subjects and what we can do to enhance the practice in an ethical context.

**Conclusion:** Development of a system through which we could warrant all rights of study participants in all cases around the world seems far from view. However, if we are in doubt about the ethics of a clinical trial, we can ask ourselves: “what would we do, if we were in the same position our patients are in now?”

**Keywords:** Clinical trials; Developing World; Informed Consent

*The authors declared no conflict of interest.*

### **Introduction**

Informed and contented participation of people in clinical trials, even when adverse events are not likely, is of outmost relevance. It brings about a constructive relationship between the physician and the patient, potentially maximizing the safety of the study and enhancing favorable outcomes. It also minimizes side effects and feeling of coercion and disrespectfulness by the patients. When patients actively participate in a clinical trial, they feel more responsible to follow the instructions of their physicians. They would also have good feelings associated with helping to enhance their own health as well as medical science. However, information about the participation process given to patients before clinical trials is often not properly presented, an issue that can result in serious threat to the decision-making process. It may lead to distrust in the medical system and physicians which is very destructive for the patient-physician relationship.

The importance of taking informed consent from people participating in clinical trials is well-understood in developed countries, with every effort taken to enhance and maintain the autonomy of patients and their right to make an informed choice of whether to participate or not [1, 2]. Several legislations have been formed to protect people's rights from potential abuse by pharmaceutical companies and/or investigators; although even in those countries, large fields still exist for modifications and enhancement. However, in the developing countries the land is still almost intact.

After a relatively long history of non-scientific approach to human life, the developing world has started to use scientific experimentations in the context of university-

---

\* corresponding author; Floor 3, Headquarters' Building, Baqiyatallah Hospital, MullaSadra Str., Tehran, Iran; E mail: Mojgan.fazel@gmail.com

based educational models as a necessary requirement for faculty promotion. Our aim in this article is to address the issue of how respectfully and ethically clinical trials are performed on human subjects in the developing world; and what we can do to enhance the practice in an ethical context.

## Review

### Origins of the problem in the developing world

In the medical context, there are different ways for experimentation of which we can recall in vitro research, experimental research on animals, and clinical research on human subjects. Although ethical concerns exist on almost all types of the above mentioned, our debate focuses on clinical trials on human subjects. The two major problems that are frequently encountered in clinical trials in the developing world are: shortage of medical services and lack of supportive laws that protect patients against coercive efforts. This probably results in some investigators feeling free to enter their patients into clinical trials without respecting their feelings or rights. In one case, one of the authors recalls a colleague talking about how he had got consent from his patients to enter them into a non-favorable trial: “well, if they don’t want to participate, they can go to another hospital to get the service; I am their doctor, and I know what is good for everyone!” No doubt, this happens very frequently in these countries. This does not essentially mean that the research itself is non-ethical. Proper explanation often makes the study participants feel willing to participate, but the problem is that sometimes investigators do not feel they should make an explanation. If one observes the number of patients who have potentially refused to participate in different research trials in an area, he/she can have a better estimation of how many patients have been coerced to enter the trial, in that region.

### Informed consent document development and presentation

**Case:** In an Indian study on the natural behavior of precancerous cervical dysplasia [3], authors of the study entered 1158 women, untreated, with lesions of different stages who “had not given consent for taking treatment”, into a follow up from 1976 to 1988. According to debates by the investigators from the Institute of Cytology and Preventive Oncology in New Delhi, most of the study participants were illiterate. Here, the question is whether investigators described the potential effects of patients’ refusal to take the treatment properly; and despite that, they raised over one thousand individuals for inclusion into the study?

To get a clinical trial which has been done on human subjects published in a biomedical journals, these journals ask for confirmation that informed consent has been given by every study participant. You probably have to check a check-box stating that all people enrolled in your study have provided “informed” consent for inclusion. But how much are these consents informed, and how much are they consents, at all? Documents given to people to read and sign for inclusion into a study can contain controversial material, if they have been read at all. In one study, José Granero-Molina *et al* [4] found that linguistic communication difficulties, cultural clashes, asymmetry of communication between professionals and patients, assignment of rights on the part of patients, and overprotection of professionals and institutions affect the development of consent documents and the process of getting the informed consent. On the other hand, there is no consistency between ethicists on how to develop and present an informed consent document. In a study by Matthew Hotopf *et al* [5], six local ethical committees have been asked to argue on, and edit a consent document. Analysis showed that their arguments were very inconsistent and highly variable compared to each other. Gitangali *et al* [6] have reported that only less than one third of an in-patient population was likely to give informed consents to participate in a research trial. Moreover, Pope *et al* [7] showed that subjects who reported having understood the consent information letter had better recall of placebo/active drug comparator and better understanding of why placebo was used. These facts show the complexity and multi-factorial nature of the important issue of taking informed consent. We need to design an informed consent document which sufficiently addresses different concerns of ethicists, with the least possible threat to people rights.

### Proper documentation and presentation of an informed consent

**Case:** Jesse Gelsinger was the first documented person publicly identified as having died in a clinical trial for gene therapy [8]. He was 18 years old at the time. Gelsinger suffered from ornithine transcarbamylase deficiency, a hepatic X-linked hereditary disease. He was enrolled into a clinical trial conducted by the University of Pennsylvania aiming at developing a treatment for infants born with the disease. Gelsinger was injected by an adenoviral vector carrying a normal gene, to test the safety of the procedure; but he died four days later, due to a massive immune response triggered by the viral vector used to transport the gene into his cells, leading to multiple organ failure and brain death. Although his father had given consent to participate in the trial, he had not been told enough about the risks of the procedure.

Because he did not understand some of the possible risks, he lost his son, as a result.

A proper informed consent necessitates appropriate communication prior to signing the document, through which the patient or a parent/legal representative having the custody of a child or a disabled person agrees to enter one into a clinical trial. This process, however, may not fully guarantee a complete understanding or a free right to decide. It may be done with lack of acknowledgement of some key information that may affect patients' decision to participate [9]. For example, investigators are likely to be unwilling to share information on rare complications known to be associated with the research procedure. They often argue that giving this information is unnecessary due to their rare nature, and that sharing this information with patients increases their anxiety [10, 11]. However, it has been shown that patients want to know [12, 13].

#### **Gain from the study**

One of the ethical problems that occur in developing as well as developed countries is related to gain from the study. The investigator is supposed to be concerned about the efficacy of a treatment or preventive method in enhancing the health and quality of life of the study subjects themselves, besides prospective patients. People who participate in the study must be expected to benefit from the results of the study. So, enrolling people into a research with no potential benefit for themselves cannot be considered ethical. This is a critical issue that is easily disregarded in the developing countries. Investigators should not presume that giving a consent means that you can enter people into any clinical trial.

#### **Hidden coercion**

Hidden coercion is another major concern on the ethics of the practice. Informed consent is a free and voluntary act which should be honestly and freely presented to the potential participants. People should not feel enforced to get involved into the study by their physicians, literally or non-literally. Investigators should not impose the feeling that if the patient does not admit to participate, he/she offends their physician; or he/she may not expect to receive full medical service, anymore. However, for encouraging the patients to participate, describing the importance of the research and its impact on treatment of the study subjects themselves, as well as the prospective patients is an ethical and necessary issue.

#### **Ethical issues in nephrology and kidney transplantation**

With new medical procedures introduced into kidney medicine, the overall survival of people with renal failure has dramatically improved, and as a consequence,

the number of end-stage renal disease (ESRD) patients has also increased. On the other hand, owing to more effective immunosuppressive agents employed in kidney transplant patients in the recent two decades, the outcome of these patients was significantly enhanced; and renal transplantation has become the treatment of choice for ESRD patients.

With the increasing numbers of ESRD patients and limited sources of kidney grafts from deceased donors, living donor renal transplantation has become more popular in clinical practice. One of the most tenacious ethical concerns over renal transplantation from living donors is that this procedure apparently endangers healthy individuals by exposing them to a potentially harmful procedure for saving another life. This dispute not only exists on transplantation from a non-related donor, it also applies to transplanting organs from related donors. However, while most ethicists are concerned with ethics of the procedure, few of them may consider the risk of unethical researches that may affect both kidney donors and recipients. Most kidney patients and living donors are at high risk for coercion to enter clinical trials, especially in the developing world where supportive organizations are not widely available. This issue will be of more relevance, when one considers living unrelated donors who are financially paid for donation. They might be at risk of being forced to enter research trials.

#### **Critical recommendations**

Knowing the problem and its relevance, herein we aim to present some suggestions to address the issue of making research endeavours more ethically acceptable in developing countries. For this purpose, the first step is to know and instate successful endeavours which have previously been used by the developed world. Establishment and/or empowering independent institutional review boards or ethics committees which can effectively supervise and control clinical trials might be the most important and fundamental work to be undertaken. These bodies are formally designated to review and approve research on humans. They are entrusted with protecting the rights, safety and wellbeing of subjects involved in a clinical trial, assuring the adequacy and safety of the informed consent and the clinical trial protocol and the adequacy of facilities. They typically include medical and non-medical members. On the other hand, reviewing histories for researches with unethical aspects previously performed in different countries as well as effective legal actions employed to address these cases can also help to resolve this problem. Besides all, to promote ethical aspects of research in the developing world we need international collaborative efforts. International scientific and ethics committees

must try to facilitate this process, and exert pressure on individuals and societies who refuse to respect ethics in their researches.

## Conclusion

Despite all the issues mentioned above, development of a system through which we could warrant all rights of the study participants in all cases around the world seems far from view. However, as ethicists and investigators, we have the duty to do our best to maximize respectfulness to people's right to decide on participation into clinical trials. In the context of developing world, we may have fewer instruments to apply ethical concerns on clinical trials performed in our countries, but the first step is probably to start from ourselves. If we are in doubt about the ethics of a clinical trial, we can ask ourselves: "what would we do, if we were in the same position our patients are in now?"

## References

1. Nelson RM, Merz JF. Voluntariness of consent for research: an empirical and conceptual review. *Med Care*. 2002 Sep;40(9 Suppl):V69-80.
2. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. *Hastings Cent Rep*. 2009 Jan-Feb;39(1):30-9.
3. Mudur G. Indian study of women with cervical lesions called unethical. *BMJ*. 1997 Apr 12;314(7087):1065.
4. Granero-Molina J, Fernández-Sola C, Aguilera-Manrique G. Applying a sociolinguistic model to the analysis of informed consent documents. *Nurs Ethics*. 2009 Nov;16(6):797-812.
5. Hotopf M, Wessely S, Noah N. Are ethical committees reliable? *J R Soc Med*. 1995 Jan;88(1):31-3.
6. Gitanjali B, Raveendran R, Pandian DG, Sujindra S. Recruitment of subjects for clinical trials after informed consent: does gender and educational status make a difference? *J Postgrad Med*. 2003 Apr-Jun;49(2):109-13.
7. Pope JE, Tingey DP, Arnold JM, Hong P, Ouimet JM, Krizova A. Are subjects satisfied with the informed consent process? A survey of research participants. *J Rheumatol*. 2003 Apr;30(4):815-24.
8. Teichler Zallen D. US gene therapy in crisis. *Trends Genet*. 2000 Jun;16(6):272-5.
9. Byrne DJ, Napier A, Cuschieri A. How informed signed consent? *BMJ* 1998; 296: 839-40.
10. Miller SM, Mangan CE. Interacting effects of information and coping style in adapting to gynaecologic stress: should the doctor tell all? *J Pers Soc Psychol* 1983;45:223-36.
11. Shaw RE, Cohen F, Fishman-Rosen J, et al. Psychologic predictors of psychosocial and medical outcomes in patients undergoing coronary angioplasty. *Psychosom Med* 1986;48:582-97.
12. Farnhill D, Inglis S. Patients desire for information about anaesthesia - Australian attitudes. *Anaesthesia* 1993;48:162-4.
13. Garden AL, Merry AF, Holland RL, Petrie KJ. Anaesthesia information - what patients want to know. *Anaesth Intensive Care* 1996;24:594-8.