

# INFORMED CONSENT PROCESS, THE BANE OF UNETHICAL CLINICAL RESEARCH; A REVIEW

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## ABSTRACT

Clinical Research is a branch of medical science that experiments new drug, medical device or biological on human subjects prior to approval. For the study to be credible, unbiased and generally applicable, all ICH-GCP regulations, other international and local regulations governing ethical clinical research studies should strictly be adhered to. The current regulations for clinical research are based on a combination of ethical thoughts and history. Ethics is different from law and regulation, both of which mandate a certain way of acting. The United States regulations for the protection of human subjects and other regulatory agencies from different countries have provided minimum baseline with which everyone must comply in operating an institutional review board (IRB), obtaining informed consent from research subjects and conducting research in an ethical manner.

The challenge, especially in a practical environment such as clinical research, is to translate these regulatory documents, provisions and different ethical principles into action. In clinical research, the consent of the research participants should be received before they are enrolled for trial. Many years after the document governing ethical principles of clinical research was developed and addressing three major areas: respect for persons, beneficence and justice, abuse of informed consent process has been a major ethical problem in most clinical research conducted across the globe and especially those conducted in Africa.

Is informed consent process well administered? Do these patients have a good comprehension of the entire research process? Is informed consent a mere signing of a paper to participate in a trial, or a continuous process?. Is there a better way of administering informed consent to achieve a better research outcome that will benefit all? This review shall focus on recalling history of abuses of informed consent process and ways to correct the unethical practice shall be discussed.

**Key words:** Informed Consent, Ethics, Regulations, Clinical Research

## INTRODUCTION

The emergence of new infections and the constant changing nature in the genetic components of organisms that elicit infections and disease processes have lead pharmaceutical companies to develop new molecules /drugs that will treat these diseases. The concept of evidenced based medicine, using statistics and testing has prevailed in the West since the end of 19<sup>th</sup> century (Rothman ,1991). The first formal statement of ethics was the Nuremberg code adopted after the trials of Nazi doctors in 1947 (Mitscherlich and Mielke, 1992) . Before any new medicine is approved and marketed, it should go through formal and rigorous clinical trial. The testing of these drugs are usually performed using human subjects and regulations have stipulated that informed consent should be sought prior to trial. Many scientific atrocities carried out by Scientists in the past were responsible for the development of ethical regulations in research. In 1955, an antiseptic, Stalinton, killed 102 patients in France. Thalidomide was responsible for killing 12,000 foetal abnormalities between 1957 and 1962. A powder, Morhange poisoned 145 infants and killed 36 in 1972 during trial (Shuster, 1997).

In all of these studies, the human subjects used for the studies were neither informed nor aware of the risks associated with the study. Scandals such as these led to the introduction of stringent regulations in clinical research all with a view to protecting the research subjects.

## **ETHICAL PRINCIPLES OF CLINICAL RESEARCH**

Ethical principles guiding clinical research have emanated from different regulations, reports and codes. These are:

### *The Nuremberg Code (1947)*

The modern history of human subject protection began with the discovery of the atrocities committed by Nazi physicians (Rothman ,1991; Mitscherlich and Mielke, 1992). For example, such atrocities included twin experiments, where one twin was exposed to a pathogen and then autopsied to determine the natural progression of the disease. The other uninfected “control” twin was then “sacrificed” to see what the differences were. It may constitute a very interesting comparison from a scientific perspective, but such an experiment was wholly unethical and inhumane. When these atrocities were brought to the public court, the judges at the trial had no basis in law by which to prosecute the Nazi physicians. They developed 10 principles for this purpose, and these principles formed the basis of what came to be known as the Nuremberg Code for research involving human subjects. Few highlights of the Nuremberg Code include:

- Voluntary consent is essential. This requirement is at the heart of what the Nazis did wrong. They did not ask any of the people who were subject to their experiments if they wanted to participate.
- Research risks must be minimized and relative to the anticipated benefits of the research.
- The research must benefit society. It is unethical to needlessly endanger the well being of human volunteers if other methods of investigation exist. Poorly designed human subject

research is unethical from its inception. Poorly designed research process, results in poor research outcome with possibility to endanger subjects' life.

- Research must be based on pre-clinical studies in animals and knowledge of the condition under study. Many of the Nazi experiments were performed just because the physicians found them interesting.
- Subjects have the right to end their participation in research. Unfortunately, the Nuremberg Code did not have much impact in the United States outside of the scholarly community. The reasons were simple. These then were mere codes and not legislation or laws.

### *The Belmont Report (1979)*

This was produced secondary to the Tuskegee Syphilis study of 1932-1972. The study was to last for 6 months but due to the fact that the investigators were getting "good data", it continued for 40 years. To worsen the situation, the patients were denied treatment even when one was available (David, 2004)

The Belmont Report articulated three core ethical principles:

- **Respect for persons:** This principle concerns the ability of a person to direct his/her own actions. The requirement to obtain informed consent from prospective subjects is the practical translation of this ethical principle. Capacity to consent is also important. You must ensure that the person you are asking to undergo a clinical trial has the capacity to freely authorize his/her participation.
- **Beneficence:** This principle requires a balance between minimizing harms by good study design and maximizing any benefits that might accrue to study participants.
- **Justice:** This principle asks us to take a broader view of the research. There should be an equitable distribution of benefits and burdens, with equitable subject selection. Sometimes implementing this principle can be daunting due to entrenched social inequalities and disparities that exist in our country and in the world.

### **DECLARATION OF HELSINKI, (1964, AMENDED)**

Chronological Revision of the Declaration of Helsinki (DoH)

Year	Month	City	Sections Revised	Revisions Made

1975	October	Tokyo, Japan	3rd, 4th and 5th paragraph  6th and 7th Paragraph  Others Section 1.2, 1.5, 1.8, 1.9- 1.11,1.12,11.2, 11.3,11.4,11.5	Nature and purpose of medical research  Respect for environment and for animals used in research  Review of research protocol by EC/IRB, interest of human subject to prevail over science, adherence to accuracy in publishing, enhanced requirement for informed consent, protocol to declare the adherence to DoH principles, best current therapy should be used, Assurance of access to best proven methods, patient's refusal not to affect doctor-patient relationship and when not to consider obtaining informed consent.
1983	October	Venice, Italy	Introduction, section 1.11,	Doctor changed to Physician  Consent from minor to be obtained
1989	September	Hong Kong	Section 1.2	Specially appointed committee independent of the investigator and sponsor to review study protocol.
1996	October	Somerset West, South Africa	Section 11.3	The best available treatment should be given to study subjects or control group.  Use of placebo even in the availability of proven standard treatment.
2000	October	Edinburgh, Scotland	Paragraph 8, 13, 16,21, 22,25,26,31, and 32.	Special consideration on research using vulnerable group, Ethics committee should monitor research and disclose all CoI, all studies should be publicly available, maintenance of confidentiality of subjects, provisions for obtaining consent other than in writing,

				consent changed to assent with research involving minors, provision where consent from subjects is not possible, disclose to subjects which aspect of care relates to research and use of all unproven treatment should be made available for research and results recorded and published accordingly.
2002**	October	Washington, DC, USA	Note of clarification added : section 29  Paragraph 30	“a placebo-controlled trial may be ethically acceptable, even if proven therapy is available”  Post trial care of participants: Study participants should have access to proven therapies emanating from the study.
2004**	October	Tokyo, Japan	Same as above.	Same as above.
2008	October	Seoul, Republic of Korea	Paragraph 19, Paragraph 30	Listing of clinical trial in publicly accessible database,  Publication of clinical research finding including ‘Negative’ result
2013	October	Fortaleza, Brazil	Paragraph 15, paragraph 20, & other minor changes	Increased protection for vulnerable groups, compensation for subjects harmed as a result of participating in the research, expanded requirements for post-study arrangements, use of placebo, scientific justification for the research.

*Source: Robert et al (2004), Alexander (2013)*

\*\* Just note of clarifications made on the document.

*ICH-GCP Regulation: (1996)*

**COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS) RESEARCH GUIDELINES, (2002).** All regulations stipulated adherence to informed consent Process.

### *What is Informed Consent?*

Informed Consent is the process by which a person freely confirms their willingness to participate in clinical research after having been informed of all parts of the study that are relevant to the individual's decision to participate. (ICH-GCP, 1996).

### *What Constitutes Informed Consent?*

- Competence/literacy level of the subject
- Disclosure of all information to the subject
- Understanding or comprehension of what has been thoroughly explained.
- Voluntariness of the decision

### *What are the Elements of Informed Consent:*

The Federal regulations require that 8 elements be included in each informed consent form. These are:

- Purpose and duration of participation
- Risks
- Alternatives
- Benefits
- Confidentiality of records
- Compensation for injuries
- Person to contact for answers to questions
- Voluntariness and right to withdraw

### *Abuse of Informed Consent*

Prior to the enactment of ethical regulations governing clinical research, abuse of informed consent was a major problem. Many years after different regulations have been adopted all with a view to improving the ethical practices in clinical research and improving patients' safety and right to full information in every research process, the regulations have not yielded the desired results. Abuse of informed consent has been a major problem in major trials conducted in Africa, Europe, America and Asia. Most clinical research studies have reported abuse of IC . The under mentioned case studies give some examples

### **CASE STUDIES**

- **Gene Therapy :A case study with Jesse Gelsinger (Stolberg ,1999)** : He was 18 years old. He suffered from an X-linked genetic disease. He was deficient of ornithine transcarbamylase. This enzyme is very important and critical for the conversion of ammonia, a poisonous gas in the body to urea, a deaminated product from ammonia, a reaction that takes place in the liver. The disorder is fatal in children due to the resulting metabolic acidosis secondary to the accumulation of NH<sub>3</sub>. In Jesse's case, he did not inherit the disease from his parents, but was caused as a resultant of a spontaneous

mutation of his gene which occurred after conception. His case was therefore not too fatal, but he was unable to metabolise certain foods containing protein and ammonia. On 13 September, 1999, Jesse joined a clinical trial for gene therapy run by the University of Pennsylvania. Jesse was injected with the deficient gene using a viral vector. He died during the process from injuries resulting from the trial, probably as a result of multiple organ failure. Investigations conducted showed that the gene therapy produced toxicities in human subjects used for the trial which the investigators did not disclose, but rather than terminate the study, the investigators continued with the trial .It was also discovered that the informed consent process was poorly conducted and risks associated with the trial was not properly disclosed. Jesse has high plasma ammonia and rather than excluded him from the study based on the pre determined selection criteria, he was still included in the trial.

- A research trial was carried out to check the level of malaria in children and according to the protocol, blood was to be collected once a day from each of the participating children in the clinical trial. However, rather than adhere to this protocol, the researchers went on and collected blood samples four times a day from each of the participating children. Participants were not informed of this and IRB saddled with the responsibilities to protect the subjects was also unable to detect and correct this unethical practice
- In a clinical research study that investigated the relationship between diabetes and sickle cell disease, a random check of the research process showed that: Patients were told to swallow a glucose solution and remain seated and immobile for 5 hours and blood samples were collected at timed interval over the 5hour period. Patients never knew they were being used for a research. Their consent was not sought. They were only promised a paltry sum of 3.0 USD which was neither disclosed, reviewed nor approved by the IRB.

## **RECALL OF CLINICAL RESEARCH WITH ABUSED INFORMED CONSENT PROCESS:**

In 2001, a clinical trial was conducted at a site in US on a drug, hexamethonium. This drug was previously used for the treatment of hypertension, but due to its inefficiency it was deregistered by the FDA and subsequently withdrawn from the circulation. Rather than discard the drug, the sponsors began to look at the other medical benefits of the drug on healthy volunteers using clinical trial. The drug was administered by inhalation to the healthy volunteers including Ellen Roche, a 24 year old employee of a company who died few days after the inhalation. Investigations into her death were navigated to defective informed consent process. It was found that the informed consent document was deficient in many ways. Investigations showed that the side effects of the drug were not fully documented in the informed document. The section on risks stated that hexamethonium may reduce blood pressure and may make one dizzy especially when one stands up. The major cause of death which was pulmonary toxicity was neither mentioned in the document nor disclosed to the patient (Steinbrook,2003)

In 2003, a clinical trial, Letrozole trial was conducted in India. For any clinical trial to be approved in India, it should receive the approval of the Drugs Controller General, India (DCGI), Hospital Ethics Committees and informed consent of participating subjects. Regulations also stipulated that trials should be done in recognized institutes with adequate research facilities and compensation should be given for any mishap occurred due to the trial. In this trial, more than 400 women who were unable to conceive were enrolled for a trial without their knowledge/consent. The trial was to check the ability of Letrozole to induce fertility under the impression of an expensive fertility-inducing drug. This drug patented by Novartis is a breast cancer drug and is not approved for any other use in any country. Gynaecologists in their private clinics termed as ‘institutes’ with no standard research facility did most of the trials. Though the sponsors and physicians that conducted the trial knew they violated the set standards, yet nothing was done to remedy the injustice and violations on patient’s right and safety. (Indrajit Basu , 2004; Ketan, 2005 )

Prevention of Mother to Child Transmission (PMTCT) trials was conducted in Uganda from 1997-2003 using Nevirapine (Viramune) . Reports emanating from the study showed that not only were the patients improperly informed about the study, their consent was neither sought nor received. To worsen the trial and the conditions of the patients, wrong doses of the experimental drug were administered. Records regarding the trial were poorly kept; none of the adverse events and the fourteen deaths occurred were reported. Serious Adverse Events (SAE) procedures were not followed, and Boehringer Ingelheim (BI), the sponsor of the trial pressured US National Institutes of Health (NIH) to destroy the earlier research records to avoid the audits by US Food and Drug Administration (FDA). In 2004, FDA issued warnings about the drug’s side effects and the usage on certain patients was stopped (Nancy , 2007).

In Nigeria in 1996, the drug giant Pfizer, conducted a clinical trial using Trovan, a drug developed for the treatment of cerebral meningitis. Many innocent children were given the drug and it resulted in lots of death and deformations. The informed consent was neither administered nor the consent sought from the subjects. The risks associated with the drug were not also disclosed. IRB was not properly constituted nor did it give a formal approval of the trial protocol.(Onyeaghala, 2008) .

## **SIGNS OF DEFECTIVE INFORMED CONSENT**

- Poor understanding of research process by participants
- Defective informed consent process and documentation
- Lack of informed consent
- Withholding information about risks
- Placing patients in a coercive situation
- Exploitation of a vulnerable group of subjects
- Abuse of human Right
- Financial inducement/abuse
- Deviations /violations of protocol

## **WHY DOES IT OCCUR?**

While regulatory agencies in the West and other developed countries are trying to reduce abuse of ICP in clinical research, a lot of factors make it to thrive in most parts of developing countries. These are:

- Poverty
- Weak regulatory environment
- Lack of oversight function of IRB/IEC
- Illiteracy
- Desire to get ‘POSITIVE’ findings from research and NOT ‘NEGATIVE’ findings
- Do – Not –question –me attitude of some physicians (common in some African countries)
- Inability to separate medical care from research ( either way, IC is required)
- Research Fraud
- Desire to Publish

## **CONSEQUENCES OF POOR ICP**

- Abuse of human right
- Placing participants on a greater risk
- Development of unethical drug
- Numerous Recalls of products already approved
- Legal issues – tort (civil wrong doing) or criminal law (lack of informed consent-assault & battery)
- Denial of publications from such studies

## **CAN INFORMED CONSENT PROCESS BE IMPROVED?**

- Physicians /PI should NOT administer informed consent – Conflict of interest and unnecessary coercion might be inevitable
- External ethical review of the research process other than institution’s review should be sought
- Increased oversight functions of ERC and SMB should be enhanced
- Consider differences in culture ( cultural component of IC)
- Use simple English and Limit number of pages to smaller volume
- Translate into subjects local language.
- Sponsors should insist on GCP compliant clinical research from all regions of the world
- Frequent audit of clinical research sites, procedures and processes.
- Quality assurance of process
- Use of multi-media interaction for illiterate group should be considered

## **CONCLUSION**

Regulations may be made for every process, but it is within the purview of every Scientist to do that which is right. The decision to do what is right is a major part of human existence. No matter what regulations exist, when they are not implemented, it all becomes a piece of paper.

Ethics have come a long way in research and to improve and advance scientific discoveries, increase translational research and medicine, the use of human subjects at various phases of the translational study becomes inevitable. All efforts should therefore be made to protect the subjects who have volunteered to improve the health of others.

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