ESSENTIALS OF PROTOCOL DEVELOPMENT IN HUMAN RESEARCH PROPOSALS

BY

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INTRODUCTION

Medical research involving human subjects has the primary purpose of improving prophylactic, diagnostic and therapeutic procedures as well as the understanding of the etiology and pathogenesis of disease. Africa and indeed Nigeria has experienced a flooding of research projects from funding agencies like NIH, FHI, WHO and several others. In recent years this has increased from less than 10 in 1965 to over 80 in 1999 and 1170 by the year 2000. Most of the Clinical Research trials in Africa were conducted in South Africa (565), Nigeria (98), Kenya (89),Gambia (56) and Tanzania (50). The number of foreign Human subjects participating in New drug applications (NDA) trials increased from 4,000 in 1995 to 4000,000 in 1999[1]. Several incidents of violation of human rights due to subjection to risks have been documented in the process of human subjects research[2].

Serious Human abuses have been perpetrated for over 100 years. This include the Tuskegee Syphilis experiments (1932 1973) in which 600 poor, black men with syphilis, two thirds already at advanced stage of the disease and one third at onset were admitted, given free medical attention but not treated. They were promised free meals and fifty dollars ($50) burial stipend. Despite the discovery of Penicilin in 1943, no treatment was given to these black men until in 1972, when there was a press bust. The project was subsequently halted and the Department of Human Education and Welfare (DHEW) indicted. Ten million dollar settlement was awarded in 1974 and an Advisory Committee (ACHRE)[3] was set up. In 1997 President Clinton offered a public apology to the victims and their families.

The Nazi experiment was another atrocity. From 1930 to 1945 Nazi soldiers experimented with Jeweish prisoners who were mentally ill and retarded to test their endurance levels with electric shocks, severe hypothermia, exposure to poisons, infectious diseases and irradiation to induce sterility.

The Timothy Leary and Richard Alpert experiments were conducted from 1960 to 1963. These researchers tested the effect of Hallucinogenic drugs such as LSD on human personality using friends, associates and students. They were finally stopped in 1963.

At Sloan Ketering Cancer Centre, the Jews carried out an experiment to study the effect of foreign tissue on certain body reactions. These set of experiments ware termed "harmless skin

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test" . " Live cancerous Cells" were injected under the skin of old, disabled patients with compromised immune systems.

These misconduct by doctors and researchers necessitated the MANDATE which is a set of rules and guidelines to regulate human subject research. The objective of Human subject research is to test and develop new treatment modalities to combat diseases, study and formulate public health safety policies for the social well being of people. In 1989, Alex Capron wrote " the darkest moments in medical annals have involved abuses of human subjects". History is filled with numerous stories illustrating human cruelty as well as strong advocacy for the respect of others in research activities. Emergence of a code of conduct was signed into law in July 1974 as the National Research Act. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created. The Belmont Report formally titled Ethical Principles and Guidelines was published in 1978[4].

THE MANDATE:

The mandate incorporates a series of codes of conduct which include: The Nuremberg Code, the Belmont Report, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human subjects[5], the 45CFR 46, the Helsinki Declaration[6], WHO Operational Guidelines for Ethics Committees that Review Biomedical Research[7].

The first in the series of codes of conduct is the Nuremberg Code[8]. This state that Researchers must themselves obtain Voluntary Informed Consent from their research participants. Experiments must be strictly beneficial to individuals,their communities, or the society in general. Same experiments previously conducted on animals and the natural history of the disease must be clearly identified before human subject research is commenced. There must be no unnecessary physical or mental harm, injury or death to participants. A reasonable risk/maximum benefit ratio must be maintained. Scientists must be competent and professional. Participation must be voluntary while avenues must be available for withdrawal from study without loss of patient care. Adverse events must be promptly reported to the Review Committee to effect stoppage of such studies.

The Belmont Report[4] stresses the autonomy of participants and persons with diminished capacity e.g. Fetuses, Children, Pregnant Women, Prisoners and others who must have their rights respected. Project benefit to participants must be maximized with the risk/benefit ratio adequately assessed. There must be no harm to the participants. Research must be responsive to local needs . There must be equitable justice in the selection of participants. Selection must not be based on convenience to researchers or on poverty status of participants. The community must be the beneficiary of the research carried out in their locality.

The Federal Oversight by the office of Human Research Protection (OHRP) 45 CFR 46[9] section applies to all research regulated by Federal Agency of the United States. Since our researchers in Nigeria are involved in collaborative research from the United states, we invariably have our regulations guided by this code. The 45 CFR 46 defines the functions and operations of Institutions, Institutional Review Bodies and Investigators. It establishes criteria for Exempt status. It also defines categories of protocols for expedited reviews. It classifies Vulnerable population for additional and more extensive reviews.

The international mandate incorporating these and other relevant codes of conduct is based on four key principles of Ethical guidance of: Respect for persons, Beneficence, Non

Maleficence and Justice. Respect for persons clearly denotes the autonomy of persons in deciding whether or not to take part in research projects. It clearly explains the comprehension of the consent process which is key. It states that Vulnerable population have special regulations outlined for pregnant women, prisoners, children and other decisionally impaired, poor, illiterates, employees and students. The International. Mandate spells out separate but interrelated responsibilities of the investigator, the Institutional Review Board/Committee and the Institution or Research Institute.

Despite these set of rules and regulations to guide experimentation with human subjects, a great deal of improperly conducted researches still take place especially here in Africa[10],. Notable among such misconduct is the Pfizer research on children in Kano, Nigeria in April 1996[12]. This involved the death of a 10 year old girl who died after a 3 day-free treatment from a humanitarian charity "Doctors without Boarders". The antibiotic "Trovan" used was an unapproved drug in the United State. Because Pfizer apparently could not find enough patients in US, its attention was suddenly turned to Kano among people dying of meningitis epidemic. In the experiment, Pfizer had no signed consent forms and probably the patients did not know that they were even in an experiment; they only knew they were sick and getting treatment. This is an example of corporate drug experiments conducted by private interests in Africa, with little independent oversight, while humans are used as guinea pigs, and pledge of quality medical care sometimes fatally hollow. No wonder the Washington post reported in year 2000 finding of an abundance of subjects and lack of oversight abroad, big drug companies' test overseas to speed products to market under the title: "; The Body hunters: Exporting Human Experiments". Noting that Africa has a large research population vulnerable to coercion, a special need for protection of human subjects in research is required.

If there is non compliance with ethical guidelines in the preparation of the protocols, or some changes go unreported to IRBs/IRCs or the Institution, then exploitation in Human Subjects research will continue[13]. A good example of non-compliance to Ethical guidelines is the John Hopkins University (JHU) Asthma experiments in which Ellen Roche a 24 year old employee volunteer participant died after inhaling experimental hexamethonium which destroyed her lungs. JHU-IRB and the Institution's research set up were accused of improper conduct of research and therefore its research outfit was suspended for a period of time.

The office of Human Protection (HRP) visited the institution and actions taken included

- Suspension of all Multiple Protection Assurance (MPA) on July 19,2001
- Suspension of all Federally sponsored research in JHU
- A demand for all their research protocols used in protecting human subjects including the educational training profile of IRB staff members and researchers.
- Re-evaluation of all protocols was demanded.

The oversight inspection team discovered Non compliance problems of protocol including:

- PI(Principal Investigator) did not give IRB published toxicity information on the research product
- The drug was not approved for human use
- Quality of drug was uncertain
- PI did not report for the protocol amendment after the adverse event of the previous subject.
- IRB failed to solicit sufficient information for continuing review of project
- IRB inappropriately used expedited

review of protocol:

- IRB minutes of meetings were inadequate
- IRB work flow was backlogged
- IEB was understaffed and overworked
- Some IRB members had conflicts of interest
- IRB did not approve protocol changes

Informed consent weaknesses detected are:

- Inadequate description of procedures in the protocol
- Failure to disclose drug status
- Inadequately disclosed risks.

ESSENTIAL ELEMENTS OF A GOOD PROPOSAL

The research proposal must be submitted with adequate supporting documents which give special attention to the informed consent process, documentation and suitability and feasibility of protocol[7]. Investigators need to include prior scientific reviews if any and the requirement of applicable laws and regulations well considered. The following aspects of the proposal are of paramount importance:

Scientific Design and Conduct of the Study

- The appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation), and the potential for reaching sound conclusions with the smallest number of research participants.
- The justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities.
- Criteria for prematurely withdrawing research participants.
- Adequacy of the site, including the supporting staff, available facilities, and emergency procedures.
- The manner in which the results of the research will be reported and published.

Recruitment of Research Participants.

- The characteristics of the population from which the research participants will be drawn (Including gender, age, literacy, culture, economic status, and ethnicity).
- The means by which full information is to be conveyed to potential research participants or their representatives.
- Inclusion criteria for research participants
- Exclusion criteria for research participants.

Care and Protection of Research Participants

- Qualifications and experience of investigators for the proposed study.
- Investigator's plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action.
- The medical care to be provided to research participants during and after the course of the research must be stated.
- Adequacy of medical supervision and psycho-social support for the research participants must be emphasized.
- Voluntarity of participation and withdrawal should be clearly stated.
- A description of any plans to make the study product available to the research participants following the research.
- A description of any financial costs to research participants.
- The rewards and compensations for research participants (including money, services, and/ or gifts).
- The provisions for compensation / treatment in the case of injury/disability/death of research participant attributable to participation in

the research must be clearly stipulated.

Protections of Research Participant Confidentiality

- A description of the persons who will have access to personal data of the research participants, including medical records and biological samples
- The measures taken to ensure the confidentiality and security of personal information concerning research participants.

Informed Consent Process.

- Full description of the process for obtaining informed consent, including the identification of those responsible for obtaining consent.
- The adequacy, completeness, and understandability of written and oral information to be given to the research participants, and when appropriate, their legally acceptable representative(s)
- Clear justification for the intention to include in the research individuals who cannot consent or authorization for the participation of such individuals.
- Assurance that research participants will receive information that becomes available during the course of the research relevant to their participation (including their rights, safety, and well-being)
- The provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project.

Community Consideration (where applicable)

- The impact and relevance of the research on the local community and on the concerned communities from which the research participants are dawn.
- The steps taken to consult with the concerned communities during the course of designing the research.
- The influence of the community on the consent of individuals.
- Proposed community consultation during the course of the research.
- The extent to which the research contributes to capacity building, such as the enhancement of local healthcare, research, and the ability to respond to public health needs.
- A description of the availability of any successful study product to the concerned communities following the research.
- The manner in which the results of the research will be made available to the research participants and the concerned communities.

In handling your proposal for submission therefore, some legacies [11] for ethical review clearance and approval that your protocol must have include:

- Value
- Scientific Validity
- Fair subject selection
- Favorable Risks / Benefit Ratio
- Respect for enrolled Human subjects
- Detailed informed Consent section

Finally, in the development of your protocol for Human Subjects review and approval, you must observe the MANDATE in Human Research studies to prevent problems for your Research participants, for you as an investigator, your IRB /IRC and your institution.

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