AUDIT OF PROTOCOL SUBMISSIONS TO THE UNIVERSITY OF IBADAN/UNIVERSITY COLLEGE HOSPITAL HEALTH RESEARCH ETHICS COMMITTEE (2002-2007)

A DISSERTATION IN THE DEPARTMENT OF SURGERY, SUBMITTED TO THE FACULTY OF CLINICAL SCIENCES, COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN, IBADAN, NIGERIA

IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF DEGREE OF MASTER OF SCIENCE IN BIOETHICS.

BY

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ABSTRACT

The University of Ibadan/University College Hospital Health Research Ethics Committee (UI/UCH HREC) was established in 2002 to review and approve all research proposals submitted by staff and students of the two institutions. Research proposals submitted are reviewed according to International Guidelines and the Nigerian National Health Research Ethics Code (NHREC). Since inception, there had been one audit of protocols submitted to the committee. The objectives of the current review are to determine the types of protocols submitted, the duration for review and reasons for revision and amendment.

This retrospective review of all proposals submitted to the UI/UCH HREC during a 6-year period (2002 -2007) was performed using a 25 item questionnaire. The questionnaire contained information on month and year of submission, status of principal investigator, type of funding, scope, location and nature of research. Other questions include the study design, sample size, study participants, the number of revision required before approval, reasons for revision and the time interval between submission and approval. Categorical data were presented as proportions and using frequency distribution. Student t-test was used to compare the mean time from submission of protocols to approval for protocol granted exempt approval and protocol requiring review.

The results showed that the committee received a total of 752 protocols between 2002 and 2007, out of which 728 (97%) could be retrieved for this audit. Of the 728 protocols audited, 56 (0.08%) were still under consideration while decision has been reached on 656 (90%) protocols. Six hundred and eighteen protocols were approved while 38 protocols were not approved. Clinical researches on hospital patient based in single tertiary health institution constituted the bulk of the protocol received accounting for 44.9% of the entire protocols. The principal investigators were mainly postgraduate students (67.1%) while academic staff constituted 21.3%. Thirty-three (5.3%) of the protocols were granted

exempt approval. 464 (75.1%) required only minor modifications after first review. 118 (19.1%) protocols required a second review while 3 (0.5%) required a third review. Of the 566 protocols requiring review, the main reasons for revision in 50% (283/566) was inadequate information on the informed consent form. Other reasons for revision include, use of inappropriate methodology and statistics, scientific justification, sample size calculation, inclusion criteria, inadequate information on treatment of patient. The average time from submission to approval is approximately 21 weeks (95% CI: 20 – 23 weeks); it took a shorter time for protocols granted exempt approval (6weeks, 95% CI: 4 – 8 weeks) and internationally sponsored protocols (n = 64, mean: 16weeks, 95% CI: 12 - 20 weeks). The period of time between submission of research proposal and approval is significantly affected by the need for review, number of revision and sponsoring agent ($p < 0.05$).

In conclusion, majority of the proposals reviewed by the UI/UCH HREC were submitted by postgraduate and undergraduate students (78.7%). Providing a worksheet for reviewer to hasten the process of review and increasing the number of trained reviewers and expertise available for consultation are recommended to improve the review process.

Key words: UI/UCH HREC, research ethics, protocol submission, ethical review

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CERTIFICATION

I hereby certify that this study was carried out by Eyelade Olayinka R. under my supervision at the Department of Surgery, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Dr. Ademola J. Ajuwon, (Reader)
B.Sc, MPH, PhD
Supervisor

DEDICATION

This work is dedicated to all past, present and future human participants in biomedical researches

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LIST OF ABBREVIATIONS

B. C:	Before Christ
CIOMS:	Council for International Organizations for Medical Sciences
CMAC:	Chairman, Medical Advisory Committee
CFR:	Code of Federal Regulation
DoH:	Declaration of Helsinki
FDA:	Food and Drug Administration
FWA:	Federal Wide Assurance
HREC:	Health Research Ethics Committee
IMRAT:	Institute of Medical Research and Training
IRB:	Institutional Review Board
IRC:	Institutional Review Committee
K-M:	Kaplan-Meier
MSc:	Master of Science
NAFDAC:	National Agency for Food and Drug Administration Control
NHREC:	Nigerian National Health Research Ethics Committee
NEJM:	New England Journal of Medicine
NIH:	National Institute of Health
OHRP:	Office for Human Research Protection
REC:	Research Ethics Committee
SMS:	Short Messaging System
UCH:	University College Hospital
UI:	University of Ibadan
USA:	United States of America

CHAPTER ONE
INTRODUCTION

1.1 Background

The word 'ethics' is derived from the Greek word *ethos* meaning "the set of moral principles" or "rules of behaviour". Ethics tries to probe the reasoning behind our moral life by examining and analyzing the thinking used to justify our moral choices and actions in particular situations (Faneye,2007). Ethics also examine where the underlying beliefs that impact those decisions come from.

When individuals or group of people embark on research activities there is a need to ensure that the design of the research is scientifically sound and that it is conducted in conformity to established ethical codes and guidelines because of past history of unethical practice. The Research Ethics Committee (REC) or Institutional Review Board (IRB) as they are called in the United States of America (USA) is a group of persons charged with the responsibility of ensuring that scientific enquiries are conducted within generally acceptable ethical norms. The REC plays an oversight role and provides a third party independent review of research protocols to ensure safety of research participants and adherence to international codes of ethics including the Nuremberg Code, the Declaration of Helsinki, the Belmont Report and the Council for International Organizations for Medical Sciences (CIOMS) guidelines.

1.2 The role of ethics review committees

The European Union in a directive had defined an ethics committee as

> An independent body in a member state, consisting of healthcare professionals and non-medical members, whose responsibilities it is to protect the rights, safety, and well being of human subjects involved in a trial and provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigator and the adequacy of the facilities, and on methods and documents to be used to inform trial subjects and obtained their informed consent' (Directive 2001/20/EC of the European Parliament and of the Council).

It can be deduced from the definition above that in instances where research involves human participants, the role of an ethics committee is to ensure that the research protects the privacy, safety, social sensitivities and welfare of participants and minimises the potential physical, psychological, social or cultural risks inherent in the study proposal. In addition, the research proposal must be scientifically valid with rigorous methodology as poorly designed projects do not justify the commitment made by participants. The RECs inevitably have to review a range of different types of studies. Some of the studies may affect the welfare and interests of humans directly while others by their nature could have indirect impact on the participants and their communities. Thus the ethical issues that surround a study are determined partly by the nature of the study, and partly by the scientific justification for the study. These roles of RECs could be advisory, regulatory or both depending on the nature of the study protocol.

1.3 Composition of Health Research Ethics Committee (HREC)

The HREC comprise a group of persons appointed by an institution that is charged with the responsibility of carrying out scientific and ethical review of study protocols before the commencement of the research. A HREC must be multidisciplinary in composition, age and gender balanced and must include a representation from the community. The committee must function independent from control by the institution that set it up.

1.4 Statement of the Problem

The UI/UCH HREC had been in existence since the early 1980's and was granted a Federal Wide Assurance number FWA00003094-U in May 2002 by the American Office for Human Research Protection (OHRP) (Falusi, 2006). The HREC was also registered with the National Health Research Ethics Committee (NHREC) in 2007.

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The UI/UCH HREC reviews and gives approvals as appropriate for all research protocols involving human participants including the use of human specimens, tissues, embryos, foetal materials or surveys (Guidelines for ethical review UI/UCH IRC, 2005). The committee was designed to provide independent review of all research projects executed by staff and students of the two institutions whether such research are conducted independently or in collaboration with external agencies or institutions prior to the commencement of the study. The UI/UCH HREC review thereby serves to minimize conflicts of interest, protect the welfare of human participants through attention to risks, benefits, informed consent and avoiding exploitation of vulnerable individuals and populations (Kass et al 2007).

The UI/UCH HREC is independent of the College of Medicine and reports to the University of Ibadan through the Board of the Institute of Medical Research and Training (IMRAT) in the College of Medicine, University of Ibadan. The committee had been structured to a 22-member committee, with 5 Alternate members to function in the absence of regular members. The statutory members of the committee include the Chair who also doubles as the director of the Institute of Medical Research and Training (IMRAT), a Co-Chair who is also the Chairman Medical Advisory Committee (CMAC) of the UCH, a Legal officer and a statistician. Other members of the committee include representatives of each Faculty in the University of Ibadan, the community, a secretary and other alternatives. The committee holds its statutory meetings on the third Thursday of each month with additional meetings as required. The quorum for each meeting is one-third of membership (7 members) including one lay person as stipulated in the UI/UCH HREC guideline and the NHREC National Code of Health Research Ethics. The NHREC National Code of Health Research Ethics stipulates that each HREC shall have at least five members (Section D (b)) and at least one person whose primary concerns are in the non-scientific areas (Section D (e)). Furthermore, the NHREC code states that "Except when an expedited review procedure is used, research proposals shall be considered at

egularly convened ordinary meetings of HREC at which a majority of the members are present, including at least one member whose primary concerns are in non-scientific areas" {Section E (b)}. The UI/UCH HREC reviews both the ethical and the scientific aspects of the proposal submitted to its secretariat (which has four members of staff) in accordance with the NHREC code.

There had been two chairpersons since the inception of the UI/UCH HREC in 2002, two guidelines has emanated from the HREC and one published report on the establishment of the committee and an overview of its activities (Falusi et al 2007). The published report detailed all steps taken and phases involved before the HREC was actualised, in addition an overview of the activities of the ethics committee was provided. It become necessary to provide additional information to the published report in order to reveal details such as: the characteristics of the protocol submitted including the cadre of the principal investigator, funding agency, study design, sample size, and nature of research. Moreover, the details of human participants involved in the research and research sites are provided, variation in approval time was statistically analysed and reasons for amendments and disapproval documented.

1.5 Objectives

The objectives of the study are to:

1. Document the number of submissions received during each of the years under review
2. Describe the types of proposals submitted to the IRC for review during the period under consideration
3. Describe the process of review with respect to duration of each review
4. Describe the profile of investigators who had submitted proposals during the period under consideration

1.6 Significance of the study

The outcome of this study will:

1. Contribute to bridging the gap in knowledge as regards the nature of protocols submitted to the UI/UCH HREC
2. Give more information on the study design and sampling procedures employed by researchers at the University of Ibadan and the University College Hospital with a view to discuss their implications for the involvement of human research participants
3. Help in the determination of training needs of prospective researchers, reviewers and HREC members and discuss how these needs can be addressed
4. Stimulate further research on HREC activities in other parts of Nigeria

1.7 Study Limitation

The researcher did not have access to all the protocols eligible for review because some protocols were still being held by the reviewer and/ or awaiting committee review hence they could not be analyzed.

CHAPTER TWO

LITERATURE REVIEW

The independent review of research proposal by the research ethics committee is necessary to ensure valid scientific and ethical justification of the research especially when human participants are involved. The Health Research Ethics Committee must consider the risks to participants, the anticipated benefits to the subjects, the importance of the knowledge that may reasonably result and the informed consent process to be employed (Dunn & Chadwick, 2002).

2.1.1 History of human subject abuses

There were many documented unethical conduct of experimentation in humans including the German Nazi experiments (19391944), the Jewish Chronic Disease Hospital Study (1963), the Willowbrook Study (1963 – 1966), the Tuskegee Syphilis study (1932 -1972), the Trovan study in Nigeria (1996) and many others. However, details of the five human subject abuses mentioned are summarised below:

The German Nazi experiments (1939-1944): The prisoners in Nazi concentration camps during World War II were forced to undergo experiments that include exposing them to extreme temperatures, mutilating surgery, and lethal pathogens. These experiments killed and maimed many prisoners of war and the public outcry that followed this criminal scientific enquiry culminated in the 1946 Nuremberg Doctors' Trial. The doctors were found guilty of murder, torture, and other atrocities.

The medical personnel (defendants) involved argued that voluntary participation by human subjects in medical experimentation was not the norm at that time but the judges agreed with the prosecution and in addition to sentencing the defendants also

enunciated what is now known as the Nuremberg Code. The main components of the code are requirement for voluntary participation, informed consent, favourable risk/benefit analysis and the right to withdraw without penalty (McGuire, 2002).

The Jewish Chronic Disease Hospital Study (1963): This study was undertaken at the New York's Jewish Chronic Disease Hospital to understand whether the body's inability to reject cancer cells was due to cancer or debilitation. The researchers allegedly believed that the debilitated patients would also reject the cancer cells but at a substantially slower rate when compared to healthy participants. Consent was given orally but the patients were not informed that live cancer cells would be injected into their bodies because the researchers felt that this would unnecessarily frighten them. In the course of reviewing this study by the Board of Regents of the State University of New York, it was found that the study had not been approved by the hospital, the investigators had not obtained valid informed consent and that the physicians responsible for the patients' care had not been consulted. The Board of Regents (Governing Council) of the University of the State of New York argued that while therapeutic privilege may justify non-disclosure in a physician-patient relation, same is not true of researcher-participant relationship (Lerner, 2004). This case, among other things, highlighted the problem of conflicting interest for physician-researchers. The researchers were found guilty of fraud, deceit, and unprofessional conduct (Beauchamp & Childress, 2001).

The Willowbrook Studies (1962 – 1966): This is a typical story of abuse of vulnerable children. These studies were conducted at the Willowbrook State School for mentally retarded children in order to gain an understanding of the natural history of infectious hepatitis under controlled circumstances. In the course of the studies, newly admitted children were deliberately infected with hepatitis virus. The researchers defended this action by pointing out that the vast majority of the children would acquire the infection

anyway while at Willowbrook, given the crowded and unsanitary conditions. Consent was obtained from parents but critic found that during the course of these studies, Willowbrook stopped taking in new patients, claiming overcrowded conditions. However, because the hepatitis program occupied its own space at the institution, it was able to continue to admit new patients. Thus, in some cases, parents found they were unable to admit their children to Willowbrook unless they agreed to their participation in the studies. This is a demonstration of important questions about the validity of voluntary consent, the parents were coerced into giving consent by closure of the ward and there was inadequate disclosure of the involved risk. (Beauchamp & Childress. 2001)

The Tuskegee Syphilis study (1932 -1972): This study designed to take advantage of an epidemic of syphilis among the black population was conducted at Tuskegee by the United States Public Health Service to discover the natural evolution of syphilis infection in black males. More than 400 black men with syphilis participated, and about 200 men without syphilis served as controls. The men were recruited without informed consent and, in fact, were misinformed that some of the procedures done in the interest of research (e.g., spinal taps) were actually "special free treatment."

In 1936, when it was clear that many more infected men than controls had developed complications, the study had continued. Ten years later, a report of the study published in medical journal indicated that the death rate among those with syphilis was about twice as high as it was among the controls. However, the study continued despite the high mortality among research participants and no treatment was given to men with syphilis despite the fact that penicillin had been found to be effective in the treatment of syphilis in the 1940s.

The first accounts of this study appeared in the national press in 1972 following the revelation of one of the participating nurse called Rivers. The resulting public outrage

led to the appointment of an ad hoc advisory panel by the US Department of Health, Education and Welfare to review the study and advise on how to ensure that such experiments would never again be conducted. Among the recommendations was the request that Congress establish a "permanent body with the authority to regulate, at least, all federally supported research involving human subjects." It was only in 1997 that a public acknowledgement of Government responsibility was made by President Bill Clinton, and the compensation of surviving participants and the families of deceased participants continues (Beauchamp & Childress, 2001).

The Trovan study in Nigeria (1996): This is a study that took advantage of an epidemic of meningococcal meningitis in 1996, in the city of Kano, Nigeria. Epidemic meningococcal meningitis is a disease that is not seen in the United States as it typically occurs in impoverished areas causing significant mortality and morbidity. During the outbreak, many children were at risk of death from meningococcal meningitis and Pfizer's antibiotic, Trovan (trovafloxacin), was made available free of charge for the patients.

The purpose of the Nigerian study was to determine the effectiveness of Trovan in treating epidemic meningococcal meningitis. The fact that the treatment was experimental was explained to the parent or guardian of every patient in two languages—English and the local language, Hausa—by local bilingual nurses before the treatment were administered. Pfizer claimed it was not possible to gain consent from all parent because of the life-threatening epidemic, and the low literacy in the community. Following investigation on the activities of Pfizer during this epidemic by the Nigerian government, the panel concluded that Pfizer never obtained authorization from the Nigerian government to give the unproven drug to nearly 100 children and infants. Pfizer selected the patients at a field hospital in the city of Kano, where the children had been taken to be treated for an often deadly strain of meningitis. At the

time, Doctors without Borders were dispensing approved antibiotics at the hospital. Pfizer's experiment was pronounced an illegal trial of an unregistered drug by a US law court where hearing on the case had continued (Annas, 2009).

2.1.2 Historical perspective of Research Ethics

The Hippocratic Oath (c. 400 BC) prescribed that the health of the patient be the sole concern of the physician and advised the latter to "abstain from whatever is deleterious or mischievous". In medical ethics, the Hippocratic Oath clearly expresses an obligation of non-maleficence and an obligation of beneficence: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them."(Beauchamp & Childress, 2001). The maxim 'Primum non nocere' meaning 'First do no harm' is often proclaimed the fundamental principle in the Hippocratic tradition of medical ethics though it does not appear in the Hippocratic oath.

Until the early 19th century medical interventions or experimentation on human beings was uncontrolled and unregulated. For instance, in 1776 Edward Jenner had inoculated children in his neighbourhood with cow pox, an experiment that led to the discovery of the small pox vaccine. But in 1803, Thomas Percival (1740-1804), a physician from Manchester in England, elaborated what arguably is the first modern code of medical ethics. He is reputed to have coined the expression "medical ethics". He recommended that "...new methods of surgical treatment should be devised but ... should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts ...[and] previous consultation of other physicians or surgeons, to the nature of the case". He prescribed good methods and competent investigators, but was silent on ethics and informed consent.

William Beaumont (1785-1853) was perhaps the first person to mention informed consent. W. Beaumont was a surgeon in the US army who became known as the "Father of Gastric Physiology" because of his researches on human digestion. He

underlined the need for a methodological approach as opposed to a random approach in experimentation. Investigators had to be conscientious and responsible and should discontinue any experiment if it caused distress or if the subject at any time objected or became dissatisfied.

The Prussian Directive: The first "national guideline" on health research ethics was a ministerial directive issued by the Prussian Ministry of Health in 1900 following public debate on human subject experimentation, provoked by a scandalous immunization study conducted by Professor Neisser. Professor Neisser had inoculated three healthy prostitutes with the syphilis virus without their consent and all three got infected with the virus. The Prussian government took an important step by issuing a Directive "absolutely prohibiting" experimentation on minors and incompetent adults. It also imposed unequivocal consent of research subjects after due explanation of the possible adverse consequences of the experiment as a requirement. Also, only a certain qualified group of people were allowed to do research and they had to keep appropriate written records.

Despite these regulations, ethical controversies continued, in 1930, in the city of Lubeck, Germany, 77 out of 256 children died from contaminated vaccination. This incident led to the earliest controversies about therapeutic and non-therapeutic research. On February 28, 1931, Germany enacted arguably the first national research ethics regulations –"Regulations on New Therapy and Human Experimentation". This was largely in response to the increasing use of human participants in research being driven by the strength of the German health research and chemical industry. Questions about nature of appropriate information, bona fide consent, careful research design, special protections for vulnerable subjects were all carefully outlined. Experimentation on dying patients was completely forbidden and no other nation had such legally and morally advanced regulations at this time.

Human subject abuse scandals in the USA gained notoriety through a 1966 article of Henry K. Beecher, a professor of Anaesthesia at the Harvard Medical School, entitled "Ethics and Clinical Research", published in the New England Journal of Medicine (NEJM). In the article, Beecher listed and described 22 clinical studies which had violated basic ethical principles of research on human beings. Henry Beecher's challenge in the USA eventually led to the appointment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research.

The ethical principle of Respect for person ensures autonomy of the individual in deciding whether to take part in a study or not. Since the Nuremberg Code was created, informed consent has been at the forefront of biomedical ethics. An Informed consent is an individual's autonomous authorization of participation in research, and the researcher has an obligation to disclose information to participants before obtaining informed consent (Beauchamp & Childress, 2001). Informed consent is necessary to protect research participants from manipulation and abuse during the research process. Hence IREC are necessary as an independent review organ to ensure fairness between the researcher and the research subjects.

In the course of the review process, the HREC review and approval must be in compliance with federal regulations and international codes of ethics and guidelines. The main messages in each of the international code of ethics are discussed below:

2.2 The International Codes of Ethics

2. 21. The Nuremberg Code

The Nuremberg Code was established in 1947 as a result of the American military tribunal which was opened on December 9, 1946 for the trial of 23 leading German physicians and administrators for conducting medical experiments on prisoners of war without their consent. Most of the World War II prisoners used as subjects in the

experiments died or were permanently crippled as a result of these atrocities. The Nuremberg Code was the first international document which advocated voluntary participation and informed consent stipulating that 'the voluntary consent of the human subject is absolutely essential'. This means that the person involved should have the legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion. However, the responsibility for ascertaining the quality of the consent rests upon the investigator without a third person or body intervention and no force of law or penalty for offenders. Hence the code did not have much impact as it was disregarded by many investigators as evidenced in other human participants' researches including the Jewish Chronic Disease Hospital Study, the Willowbrook Study and the Tuskegee Syphilis study. The disregard for this code by investigators made the oversight function of the HREC imperative.

2.2.2. Declaration of Helsinki

In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects known as "Declaration of Helsinki". The Declaration of Helsinki (DoH) had its roots in the Nuremberg Code. Fluss identifies 12 markers of ethical research within the Nuremberg Code and noted that out of these, 10 markers appear in the original DoH and two markers were abandoned (Fluss, 1999). The Nuremberg requirement that 'The voluntary consent of the human subject is absolutely essential' is changed and the DoH allowed consent to be given by the 'legal guardian' in cases of 'legal incapacity'. The other abandoned 'marker' was the statement 'During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible'. This statement was eliminated in the DoH and appears to be covered most closely by the

sentence: 'The investigator or the investigating team should discontinue the research if in his or their judgement it may, if continued, be harmful to the individual'. In addition, the subject or subject's legal guardian has freedom to withdraw consent at any time (World Medical Association Declaration of Helsinki, 1964.)

The 1964 DoH also states 'In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research'. Hence, there was a fundamental structure of the paragraphs of the 1964 document and the first four revisions of the DoH into four headings: 'Introductory statements', 'I. Basic principles', 'II. Clinical research combined with professional care' and 'III. Non-therapeutic clinical research'. This structure persisted until the Edinburgh (2000) revision when it was substantially revised.

The DoH had been revised five times, in 1975 (Tokyo), 1983 (Venice), 1989 (Hong Kong), 1996 (South Africa) and 2000 (Edinburgh). The important additions to the first revision in Tokyo (1975) were the requirement for an independent committee review of research protocols and an elaboration of the requirement for informed consent (Carlson et al 2004). The 1983 revision effect minor changes to the document as regard terminology where the word 'doctor' was changed to 'physician', and the Latin phrase 'Ulneriori' was changed to 'especially'. In the 1989 revision, protocols were now to be 'transmitted' to a specially appointed committee independent of the investigator for consideration, comment and guidance provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed. The 1996 and 4th revision to the DoH occurred consequent to the controversy surrounding the use of placebo controls in studies of materno-foetal Human Immunodeficiency Virus (HIV) transmission. The addition to paragraph 11 section 3 states as follows: 'In any medical study, every patient, including those of a control group, if any, should be assured of the best proven

diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists'. Other major changes were as outlined by Carlson and colleague (Carlson et al 2004).

The 5th revision to the DoH in Edinburgh in the year 2000 had been the most controversial revision because the entire document was restructured and consideration for human participants is now considered to take preference over the interests of science and society. Moreover, the 2000 version no longer has any specific section dealing with non-therapeutic research and in clinical trial studies, the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods as against the 1996 version where it stated that "The potential benefits, hazards and discomfort of a new method should be weighed against the best current diagnostic and therapeutic methods'(Carlson et al 2004).

It is clear from the foregoing that various revisions to the DoH arose as new challenges and understanding of research ethics evolved. The current version of the DoH had continued to generate debates and controversy leading to arguments and counterarguments in support and against the new revision. Such debates include the definition of standard of care especially as regard clinical trial in developing countries (Nuffield Council on Bioethics, 2002), placebo-controlled trials study and other issues. The Nuffield Council on Bioethics concluded that the interpretation of 'best proven' is that 'the minimum standard of care that should be offered (in the control arm) is the best intervention available as part of the national public health system'. In their argument for the support of a placebo-controlled trial, Emanuel and Miller cited an example where a well designed placebo-controlled trial should be satisfactory on ethical grounds provided patients are well monitored for worsening symptoms, that appropriate 'rescue' or 'escape' medication is available, and participants are fully aware of their right to withdraw from the trial at any time (Emanuel et al 2001).

The HREC would need careful considerations and caution in the application of the current version of the DoH in the course of their function as an independent reviewer of research protocols to ensure a fair review process.

2.2.3 The Belmont Report

The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research prepared the Belmont Report in 1979 in the United States of America. The Report is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surrounds the conduct of research with human participants. The United States government established the National Research Act, which led to the Belmont Report following the public disclosure of the Tuskegee syphilis experiments (Macklin, 2005). The three basic ethical principle covered in this Report include respect for persons, beneficence and justice. In applying the principle of respect for persons, research subjects must be given the opportunity to choose to participate in the study and to voluntary withdraw if they are not willing to continue with the study. The principle of respect for person was stated formally by Immanuel Kant: "So act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as a means only". This statement perceives each person as an autonomous agent capable of deliberation about personal goals and of acting under the direction of such deliberation. However, it is a common knowledge that not every human being is capable of self-determination, some individual as a result of age (children), social status, level of maturity, marriage, imprisonment, illness or mental disability are incapacitated and therefore cannot exercise self-will. In such instances where individuals are not able to assert self-determination, other codes of ethics such as Doll allowed for surrogate decision and hence legal guardian consent since the principle of respect for person formed the for informed consent.

The elements of the informed consent include competence, disclosure, understanding, voluntariness and consent. One gives an informed consent to an intervention if one is competent to act, receives a thorough disclosure, comprehends the disclosure, acts voluntarily and consents to the intervention (Beauchamp & Childress, 2001). Ensuring an informed consent by human participants in a research does not

necessary implied that the details of the research are completely understood by the consenting person because each individual would have reasons or justification for participating. The weight apportioned to risks and benefits would defer among participants depending on circumstances surrounding their existence. For instance, while people of poor finances may participate in research activities because of monetary benefits or access to free medical care, others with good finances may participate due to potential health benefits of the research. The threshold for withdrawal from study participation would be determined by the compelling reasons for consenting: improving health status, continuing financial gains or both. In addition, obtaining informed consent could be perceived by the investigator as fulfilling the law and complying with code of ethics rather than respect of the autonomous persons.

Beneficence is applied in the assessment of risks and benefits to the research subjects. Research should maximise possible benefits and minimize possible harms. The principle of beneficence is firmly embedded in the ethical tradition of medicine. As Hippocrates observed in the Epidemics, "As to diseases, make a habit of two things – to help, or at least to do no harm" (Jonsen, 1978) The principle of beneficence could be interpreted as creating an obligation to secure the well-being of individuals and to develop information that will form the basis of our being better able to do so in the future.

Beneficence seems to support therapeutic research in clinical practice when participants may likely benefit from the research with the risks being the potential adverse effect of diagnostic or therapeutic treatment. Whereas, non-therapeutic research may be perceived as exposing individual to unnecessary risk mainly for the sake of advancing science or knowledge as was the case in the Nazi experiment and the Tuskegee syphilis study.

Since the main aim of basic biomedical research is to gather scientific knowledge that may or may not eventually lead to diagnostic methods, treatment methods and/or medical products, explaining knowledge as a potential benefit to participants could be a challenge. This is further complicated by the fact that the tangible benefits may materialize long after the biomedical research was conducted. In the review process therefore, the HREC should

identify clear benefits to the participants (or the society) and not only the scientific basis for the study.

The principle of justice requires a fair sharing of burdens and benefits; a formal statement of the principle is generally attributed to Aristotle; "Equals ought to be treated equally and unequals unequally." The HREC during the review process must determine who deserves to receive which benefits and who receive which burden. Justice is also applied in the selection process; the HREC is to insist that the subjects selected for research are not selected due to a history of acquiescence, and that these subjects are not, by their participation, excluded from the benefit of the treatment if it should prove successful. The research subjects must not be made to bear unnecessary burdens. The United States adopted the Code of Federal Regulations (CFR) that provide for additional subject protections shortly after the release of the Belmont Report (1979).

2.2.4. Council for International Organizations of Medical Sciences (CIOMS)

This guideline was first issued in 1982 and had been revised twice in 1993 and 2002. The guidelines relate mainly to ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health-care services. Like those of 1982 and 1993, the 2002 CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms. A particular aim is to reflect the conditions and the needs of low-resource countries, and the implications for multinational or transnational research in which they may be partners.

On informed consent, unlike the Belmont Report which was based on philosophical principles, the CIOMS guidelines state that informed or valid consent must address three questions: (*1*) does the patient have the capacity to consent?, requiring consideration of such issues as age, maturity, cognitive ability; (*2*) is the consent voluntary? (i.e. is the decision made free from coercion, inducement, or intimidation including pressure from a family member); and (*3*) has the patient received sufficient information on which to base his/her decision?

The CIOMS guidelines also stress that consent is a process, not an event. Patients need to have time to study information and ask additional questions before being asked to make a decision. Information should be available in appropriate languages and written in a style that is understandable by patients, taking into consideration relevant factors, including cultural differences. In addition, the CIOMS guidelines stipulate that the consent process must be documented, and the use of biologic materials, including their possible storage and future use and whether the material will be anonymized, needs to be frankly discussed (Macrae, 2007)

The CIOMS guidelines are quite detailed and contained important criteria for the informed consent including provision of a checklist. However, the need to document the informed consent process poses a challenge in a developing country such as Nigeria where many adults are uneducated and illiterates and may not be willing to sign a document for fear of legal implications.

The CIOMS guidelines also addresses the issue of research in the vulnerable groups including those who are economically or educationally disadvantaged, employees, those who are physically impaired, those with life-threatening conditions or seriously debilitating illnesses, those who are mentally disabled/cognitively impaired, non-native language-speaking subjects, nursing home residents, pregnant women, prisoners, university students, and wards of the state. The strict application of the Belmont principle of respect of persons may exclude some vulnerable group from research participation, however, with the CIOMS guideline; research in this group is ethically justified. Applying

the CIOMS guideline, clinical study may be justified in the interests of equity, if the research cannot be conducted in a non-vulnerable population.

2.3 Nigerian National Code of Health Research Ethics

The Nigerian National Health Research Ethics Committee (NHREC) was re-constituted in September, 2005 and formerly inaugurated on 5th October, 2006 by General Olusegun Obasanjo (rtd), the President, Federal Republic of Nigeria (Lambo 2006). The Nigerian National Codes of Health Research Ethics (NHREC 2007) is tailored towards the seven requirements proposed by Emanuel and colleagues (Emanuel et al 2000). Drawing on the basic philosophies underlying major ethical codes, declarations, and other documents relevant to research with human subjects, Emanuel and colleague proposed the following 7 requirements which make clinical research ethical

1. Value-enhancement of health or knowledge must be derived from the research
2. Scientific validity - the research must be methodologically rigorous
3. Fair subject selection- scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects
4. Favourable risk-benefit ratio- within the context of standard clinical practice and the research protocol, risk must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks
5. Independent review- unaffiliated individuals must review the research and approve, amend, or terminate it
6. Informed consent- individuals should be informed about the research and provide their voluntary consent

7. Respect for enrolled subjects- subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored.

Therefore, research proposal that does not meet the requirements as specify in the National Code except for researches that are exempted risk being disapproved. Only the HREC can determine which research is exempted.

2.4 Functions of the UI/UCH HREC

The HREC functions is tailored towards ensuring that risks of human subjects participants are minimised to the extent possible, that risks are reasonable in relation to anticipated benefits through an appropriately study design and sample size. In addition the committee ensured that there had been fair and justified subject selection, appropriate consent procedures and confidentiality of data and subjects are ensured. The committee had produced written guidelines and procedures for submission of research protocol to ensure compliance with its directives and facilitate its proper functioning. The other function of the HREC include holding regular meetings and keeping minutes of such meetings, documentation of communications with investigators, approve research before implementation, disapproval of researches that violate ethical principles and monitor research project during implementation.

Apart from paper functions of the committee, many of the activities of the HREC are stored in computer based software and devices and the use of modern means of communication such as short messaging system (SMS) through cell phones and e-mails has improved the efficiency of the HREC. The records of the modern means of communication including e-mail letters and SMS are captured and stored at the UI/UCH HREC secretariat. Protocols are retained in hard and soft copies at the secretarial office following review and approval.

2.4.1 Funding of the UI/UCH HREC

The committee is self-sustaining as it has to generate funds for the day to day running of the secretariat and its activities. Towards achieving its set objectives and goals; the HREC has system of charging for protocols submitted for review. Internationally and industrial funded research are charged up to N30, 000 per protocol while members of staff are charged N5000 per protocol submitted. Undergraduate, postgraduate and resident doctors pay a flat rate of N2, 500 per protocol submitted. Fund generated from the processing fees is barely adequate because there is no subvention from the authorizing institutions; the committee had to devise means of generating additional income through organization of workshops and seminars.

2.4.2. Protocol Review Process at the UI/UCH HREC

Research proposal submitted to the UI/UCH HREC are reviewed according to International Guidelines and Codes such as The Belmont Report, 1979, Council for International Organizations of Medical Sciences (CIOMS, 2002), Declaration of Helsinki and the Nuremberg Code. Moreover, there is also the Nigerian National Code of Health Research Ethics of NHREC which came into existence in 2006. The NHREC was established to provide the National Framework that would ensure that the Nigerian people are not used merely as guinea pigs for testing new drugs and technologies (Lambo 2006). The regulatory definition of the term research is

> a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" while the term human subject means " a living individual about whom an investigator(whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (NHREC 2007)

The guideline and regulations contained in the Nigerian National Code of Health Research Ethics (www.ulrss.net) include general rules of setting up HREC and terms of operation of such. In line with the Nigerian National Code and some minor variations suitable for a

ertiary research institution, the summary of the guideline for submission of proposal for ethical review by the UI/UCH HREC is as follows:

1. Submission of 4 paper copies of research protocol which should have a cover page that shows the title of research and corresponding investigator; background to the study, rationale for the study; objectives and research methodology.
2. Principal investigator's Curriculum Vitae in NIH Bio sketch format
3. Supervisor's attestation statement in student's research
4. Co-investigators attestation statement
5. Letter of sponsorship where applicable
6. Materials Transfer Agreement where samples will be shipped out of Nigeria
7. Clinical Trial Agreement where research is being conducted on behalf of a sponsor
8. One page plain language summary of the research
9. The informed Consent Form (a prototype of which was provided)

Submission

The first step in the HREC review is the receipt of a complete protocol containing all the material that the committee needs to perform a meaningful and comprehensive initial review. In the UI/UCH HREC, a prospective investigator requires to obtain an application form, fill and submit same to the secretariat office of the committee. Four hard copies of the protocol, a soft copy in a CD-diskette, a covering letter to the Chair of the committee, brief curriculum vitae of the investigator in NIH format and receipt of payment of the appropriate fee would also be submitted at the same occasion. The following information must be included in each protocol: a title page detailing the title of the proposed research, name of the principal investigator and others, the academic degree and departmental affiliations of each investigator and correspondent address. An attestation page containing the signatures of all participating investigators is also included. The protocol would have a

summary page, background information on the proposed study, discussion of preliminary studies result, specific aims and hypotheses, participant recruitment methods, study location, eligibility criteria, the proposed plan for research (methodology), plans for data analysis, adverse event reporting and monitoring, ethical considerations (informed consent process, confidentiality, beneficence and non-maleficence), references and data collection instrument.

Protocol Pre-review

The protocol are pre reviewed by the trained secretarial staff to ensure that all required information have been provided in the submitted protocol. Determination of which protocol requires full-committee review and which may be reviewed via the expedited process is an important task performed by the HREC Chair or a designated member of the committee. It is the responsibility of the HREC Chair to determine the type of review require for a specific protocol and to act according to the NHREC code.

Types of Review

Exempt Review: The identity of persons is not apparent or the data for the research is publicly available.

Expedited Review: A research project is given expedited review when the study has minimal risks. In this review, one member of the committee reviews the proposal and exercise authority of the full committee

Full Committee Review: This is a type of review in which the full committee discusses the project. One member of the committee is designated primary reviewer assisted by a second reviewer. Reviewer's present comments to the committee who takes a decision about the research, these comments are also communicated to the principal investigator. Approval for the research is granted after the committee had arrived at a decision by voting. Some

members of the committee voluntarily abstain from voting and may not vote when they have interest in the research. The decision of the majority is the committees' decision.

2.4.3 Assignment of Primary and Secondary reviewers at the UI/UCH HREC

The HREC administrative staff considers the area of expertise and potential conflict of interest in primary and secondary reviewer assignment. An HREC member is the first choice in the assignment, an alternate consultant is assigned to review the protocol if no HREC member has the required expertise.

At the UI/UCH HREC, the assigned primary or secondary reviewer is expected to have a good knowledge of what is required for ethical and scientific review of the protocol. However, it has been reported that lack of training of some members of IRB contributes to delay in the review process necessitating a training programme for the academic staff of the institutions hosting the UI/UCH HREC in 2003 and 2004 (Ajuwon & Kass, 2008).

2.5 A Prototypic Reviewers' worksheet

The reviewer worksheet is a tool that could assist investigators in performing an in-depth and thorough review according to the criteria specified by the Code of Federal Regulations (CFR) Title 45. The use of worksheet depends on institutional policy and is not mandatory. The following worksheet was developed at the Children's Hospital in Boston (Khan and Kornetsky 2006) and makes an appropriate reference point for the review process.

1. Introduction, Specific Aims, Background and Significance: The worksheet questions for the review of this section of the protocol are: is the study aims/objectives clearly specified? are there adequate preliminary data to justify the research? And is there appropriate justification for this research protocol?

Therefore, the reviewer must ensure that the objectives of the research is clearly described, there is a statement of the study hypothesis, and the plan for data collection is certain to meet the aims and objectives.

2. Drugs, Devices, and biological samples: When consideting research protocols that include the use of drugs, devices, and biological samples, the reviewer must apply the regulations of the FDA and or NAFDAC (Nigeria). The worksheet questions are: is the status of the drug or device described and appropriate (investigational, new use of an FDA-approved drug, or an FDA-approved drug with approved indications)?, are the drug dose and route of administration appropriate?, are the drug or device safety and efficacy data sufficient to warrant the proposed phase of testing?, is the significant risk or non significant risk status of the device described and appropriate? And do you, the reviewer agree with this determination? And does the protocol describe acceptable accountability, storage, access, and control of the device?

3. Scientific Design: Some institutions have a scientific review separate from the IRB, while at others, the IRB assumes full responsibility for scientific review. At the UI/UCH HREC, the IRB assumes full responsibility for the scientific review. The worksheet questions are: is the scientific design adequate to answer the question(s)? are the aims/objectives likely to be achievable within the given time period? is the scientific design (e.g. randomization, placebo controls, Phase I, II or III) described and adequately justified.

4. Research Procedure / Methodology: Reviewers must differentiate those procedures that are performed for research purpose from those that are performed for routine care or evaluation and determine whether the research is going to be conducted in a way that minimizes risks to subjects by employing procedures that are already being performed for diagnostic or treatment purposes. The worksheet questions are: are the [illegible] and

details of the research procedures accurately described and acceptable? is there a clear differentiation between research procedures and standard care and evaluation? are there adequate plans to inform subjects about specific research results that might affect the subject's health and/or decision to continue participation?

5. Inclusion/Exclusion Criteria for Subjects: Appropriate inclusion and exclusion criteria are essential in order to justify human subject participants and ensure equitable selection of subjects. IRBs are mandated to assure that special classes of subjects, especially vulnerable populations (i.e. women, minorities, and children) are included when appropriate. The worksheet questions are: are inclusion and exclusion criteria clearly stated and reasonable?, is the principle of distributive justice adequately incorporated into the selection criteria?, are minorities, women, children, or other vulnerable populations included in the study design?, is the population justified?, for subject vulnerable to coercion or undue influence, are additional safeguards included to protect the rights and welfare of these subjects (e.g. prisoners, mentally ill, economically/educationally disadvantaged, employees, own students).

6. Statistical Analysis and Data Monitoring. Reviewers should ensure that enough information has been provided to determine that the sample size and statistical power or precision associated with the sample size is adequate. The worksheet questions are: is the rationale for the proposed number of subjects reasonable? were formal sample sizes calculations performed and are they available for review? are the plans for data and statistical analysis defined and justified, including the use of stopping rules and endpoints? Are there adequate provisions for monitoring data?

7. Subject Privacy and Confidentiality: Reviewers must consider the extent to which research procedures could potentially invade privacy or breach participant confidentiality. The worksheet questions are: are there adequate provisions to protect the privacy and assure

the confidentiality of the research subject? are there adequate plans and provision to protect confidentiality of data during and after research? is the use of identifiers or links to identifiers necessary, and how is this information protected? Are these measures adequate? Does the principal specify in the protocol and consent form whether research data and information will be placed in safe keep or medical records?

8. Recruitment of Subjects: Reviewers must consider how, when and by whom participants are to be identified and approached for recruitment. The IRB must be assured that the recruitment process promotes voluntary participation and is not coercive in any way. Worksheet questions include: are the recruitment methods well defined? is the individual performing the recruitment appropriate for the process? are all recruitment materials submitted and appropriate?

9. Subject Compensation and Costs: Subject compensation may take the form of reimbursement for expenses associated with research participation such as travel expenses, lost wages, lunch and token gifts. The IRB must be certain that the compensation or reimbursement offered is not so large as to be coercive. Worksheet question include: is the amount for compensation reasonable and non-coercive? are there adequate provisions to avoid out-of-pocket expenses? is there sufficient justification to allow subjects to pay for these expenses?

10. Potential Risks/Discomforts and Benefits: Reviewers must identify the physical pain or discomfort as well as the psychologic, emotional, or sociological harm, including invasion of privacy, loss of confidentiality, harassment, and lessening of an individual's dignity. Potential benefits can apply directly to the subject or to the advancement of scientific knowledge. It is important for the IRB to evaluate the risk/benefit ratio and to understand the rational for believing the risk/benefit ratio is acceptable. Worksheet questions include: are the risks and benefits adequately identified, evaluated, and

described? Are the risk reasonable in relation to the benefits or knowledge to be gained? Are the risk minimized to the greatest extent possible?

11. Informed Consent/Assent: There is a list of required elements of the informed consent process and to simplify the process for would investigator at the UUUCH HREC a pro-forma has been designed. Each intending principal investigator submitting a protocol for review is required to adapt the specifically designed Informed Consent Form to their research. The worksheet questions include. is consent/assent required?, if yes, could it be verbal or written?, is a witness signature or an attestation required?, for parental consent, is the signature of one or both parents/guardians required?, who, when, where and how would the consent be obtained?, does the process provide sufficient time, privacy, and an adequate setting for the subject to consider participation?. Informed consent waiver may be considered in certain circumstances and if the research met some specified criteria (NHREC)

12. Other issues and Considerations: Issues such as allocation of resources, continuing review, potential conflicts of interest, and the need for additional ancillary review may be considered. IRB are expected to perform a review at least once in a year. The worksheet questions are: when should the next review occur? are there notable conflicts of interest? are there appropriate resources such as equipment, space, funding, and staff to conduct this research safely? Has the investigator assured appropriate monitoring of subjects during and after the research? If applicable, will counselling, referrals, or other support services be provided?

All the issue covered above are well covered in the UUUCH HREC Guidelines for ethical reviews (Falusi et al 2005) except that there are no worksheet questions for the assigned reviewer. The use of reviewer worksheet could serve as a quality control mechanism that

ensures that reviewers have considered all of the regulatory and institutional criteria for review and approval.

Following review of the submitted protocol, the protocol would be assigned a status depending on the decision of the committee. The status could be any of the following approval types discussed below (Falusi et al 2005).

2.6 Types of Approval

Approved: - If full approval is granted, the investigator may begin the research proposed in the protocol and an approved number is assigned to the protocol, for instance:

Pending – Conditional: A "Pending- Conditional" status may be stipulated, requiring minor modifications in the protocol and/or consent form before initiation. Executive approval can be given by the Chair once corrections have been made. No research may be started until all conditions have been met and formal approval obtained from the HREC.

Pending – Deferral: A deferral protocol must be substantially revised and re-submitted to the HREC.

Rejection: A protocol may be rejected by the HREC if it has been deferred several times and the HREC feels that the problems have not been adequately addressed, or if the protocol is not justified and posses unnecessary risk to the participants.

Conditions of Approval: Approval is given for a specified period of one year in the first instance. If the project takes longer than one year or the specified period, a request for an extension of the ethics clearance should be sought on the submission of an annual progress report. Approval is given on the condition:

- That any alteration proposed to the approved protocol is submitted to the committee for approval prior to the alterations being effected
- That a copy of the research project's final report is lodged with the Ethics Committee for its information

- That researcher notifies the Ethics Committee if and when a project is curtailed, terminated or completed
- That for a therapeutic trial study, the principal investigator notifies the Ethics Committee within seven (7) days of any adverse event or occurrence that takes place during the trial
- That research could be audited by the HREC during the research period to ensure compliance with guidelines

Approval of Research proposal submitted to IRB for clinical review may be delayed for various reasons including missing information, faulty informed consent process and lack of appropriate compensation especially in developing countries (Decullier et al 2005). In their review of the activity of French Research Ethics Committees, Decullier and colleagues reported that only 31% of protocols were approved with no request for modifications while the remaining protocols have missing information such as volume of peripheral blood being drawn, the length of subject visits, and lack of a prorated compensation plan for partially compensated research among others.

2.6 Previous Studies on Audit of Health Research Ethics Committee

There are few literatures examining the workload of a REC as regards the fate and characteristics of protocols submitted for independent review. An audit by Cookson on the workload of a local REC in Leicestershire over a 10year period revealed a steady rise in the number of protocols from 66 per year to 302 per year. A 12-month review within the 10-year audit showed that out of 277 submissions, 143(51.6%) were approved without amendment, 93(33.6%) required minor amendments and 41(14.8%) required further information (Cookson, 1992). In London, Boyce reviewed 353 applications submitted to a multi-centre REC between 1997 and 2000. 14 (4%) were approved at a first meeting of the REC, 217 (62%) were approved conditionally, and 19 (5%) were rejected (Boyce 2002).

In a retrospective cohort study of 25 French Research Ethics Committees' activities, Decullier and colleague found that clinical trial constitutes 68% of the protocols examined. Thirty-one percent of the protocols were approved with no modifications within 16days and when revisions were requested the main reasons were related to information to the patient (28%) (Decullier et al 2005).From the African region, a research study compared the workload of a South African University-based HREC for 2003 and 2007, it was noted that 60 – 70% of applications required revision while 27% (118) in the 2003 applications and 37% (205) in the 2005 applications were approved at first sitting of the committee; 75 -90% of the applications were submitted by graduate students (Cleaton-Jones, 2008).

Since the establishment of the UI/UCH HREC, an article reporting the process of the establishment and an overview of its activities had been published. In the paper, Falusi and colleague noted that over a 3year period following the establishment of the UI/UCH HREC, 500 application were received and the average period between protocol submission and approval decreased from 7.87months in 2002, to 3.69months in 2005 (Falusi et al 2007).

The average time between submission and approval of protocols varies from weeks to months depending on how often the REC committee meets, workload, staffing, and the types and complexities of the research being evaluated (Ahmed and Nicholson 1996). A perfectly written protocol according to accepted guidelines, therefore makes the work of the HREC easier, expedites the review process, and helps to ensure that research is being conducted professionally and according to ethical standards. Any gap in the information provided may prompt the HREC to pose a series of questions to the researchers until a clearer picture of the research proposal is complete enough to make the necessary determinations. The HREC ensures that the research proposals are of ethical standard before approval is given to conduct such research

CHAPTER THREE
METHODOLOGY

.1 Design of the study

This is a retrospective review of all proposals submitted to the UI/UCH HREC during a 5-year period, 2002 -2007. The study is limited to this period to allow for complete evaluation of the proposal submitted within the stipulated time allowed for research project component of the MSc (Bioethics) degree of the University of Ibadan. The study was conducted at the UI/UCH HREC Secretariat located within the Institute of Medical Research and Training (IMRAT) building, College of Medicine, University of Ibadan, Ibadan, Nigeria. All available protocols submitted within the study period were included in the study.

3.2 Ethical Approval

Formal approval for this study was obtained from the Chair of the UI/UCH HREC. The study had an exempt review and was assigned number UI/EC/09/0080 (Attachment I).

3.3 Method of data collection

Each protocol received between 2002-2007 was reviewed and relevant information extracted by the candidate using a questionnaire (see Appendix 1) and with assistance from the UI/UCH HREC secretariat assistants. Primary data was collected on a paper questionnaire using a coding system.

3.3.1 Instrument for data collection

A 25 item questionnaire was developed and used for data collection. The questionnaire is divided into three sections (see Appendix 1). Section one of the questionnaire contained information on the protocol identification number (HREC assigned number – 3-digits

number), month and year of submission. Section two comprised seventeen questions requesting information on many aspects of the protocol submitted. These questions can be divided into three groups. The first group of questions were on legal and administrative characteristics of the protocol: question 1:- Academic status of the principal investigator; question 2:- type of sponsor; questions 3 and 4:- location and type of research, question 6:- scope of research, and question 10:- characteristics of study participants.

The second group of questions were on proposed scientific characteristics: question 5:- study design, question 7:- sample size, question 8:- expected study duration and question 9:- incentives (benefits) to study participant. The third group of questions were on the review committee activities: question 11:- the number of revision required before approval (ranges from 0=none for exempt approval to 3=three revisions), question 12:- reasons for revision or modifications requested before approval, question 13:- the date of submission (day/month/year) and the date of final approval of each protocol were documented to determine the time interval between submission and approval, question 14: reasons for delay in approval, question 15:- number of amendments after approval, question 16:- reasons for amendments; and question 17:- rejected or disapproved protocol (closed) and reasons for closure or rejection.

3.4 Data recording procedure

Information gathered on the paper questionnaire was thereafter entered into Epidata version 3.1 for easy checks on data entry errors and correction. During data entry into Epidata (version 3.1), each protocol reviewed was allotted an identification number separate from the HREC assigned protocol number collected on the questionnaire. The database on the Epidata file was exported to Microsoft Excel (2003) to allow for data cleaning before being exported to Stata statistical software for analysis.

3.5 Analysis of the data

The data obtained was subjected to statistical analysis using Stata® statistical software package (Stata corp 4905, Lakeway College Station, Texas 77845, USA, version 10). New variables generated Microsoft Excel and then exported into Stata include: Time from submission of protocol to approval (Approval group), protocol status (approved, not yet approved or closed/lapsed). The academic status of the principal investigator was reduced to 5 categories under a new variable (pistat2). Categorical data were presented as proportions and using frequency distribution. Student t-test was used to compare the mean time from submission of protocols to approval for protocol granted exempt approval and protocol requiring review. Kaplan-Meier survival analysis was performed to establish probability of approval curves based on cumulative hazard function in order to study the time between the submission of the protocol and final approval (in days).

3.5 Analysis of the data

The data obtained was subjected to statistical analysis using Stata® statistical software package (Statacorp 4905, Lakeway College Station, Texas 77845, USA, version 10) New variables generated Microsoft Excel and then exported into Stata include: Time from submission of protocol to approval (Approval group), protocol status (approved, not yet approved or closed/lapsed). The academic status of the principal investigator was reduced to 5 categories under a new variable (pistat2). Categorical data were presented as proportions and using frequency distribution. Student t-test was used to compare the mean time from submission of protocols to approval for protocol granted exempt approval and protocol requiring review. Kaplan-Meier survival analysis was performed to establish probability of approval curves based on cumulative hazard function in order to study the time between the submission of the protocol and final approval (in days).

CHAPTER FOUR

RESULTS

4.1 Number of protocol reviewed

A total of 752 protocols were submitted to the UUUCH HREC Committee within the study period (2002 – 2007). However, 728 (97%) files could be retrieved for this audit. The remaining 24 protocols were not available because they were returned to investigators for re-submission. Of the 728 protocols audited, 56 protocols (0.1%) were still under consideration while decision has been taken on 656/728 (90%) protocols. Submission of 16 protocols was closed due to prolonged non-response from principal investigator following the initial review. The number of protocols submitted each month is as shown in table 1.

Table 1: Monthly submissions of protocols

Month	2002	2003	2004	2005	2006	2007
January	1	8	16	4	13	15
February	0	1	17	14	7	10
March	1	0	11	8	7	9
April	0	2	9	9	6	11
May	0	6	12	20	14	13
June	3	13	14	20	14	5
July	7	16	14	12	10	18
August	4	10	14	19	5	9
September	15	11	7	16	11	10
October	10	12	7	8	10	4
November	11	8	10	20	13	7
December	10	19	27	9	12	10
Total	62	106	158	159	122	121

There was an increase in number of submission in June and July for the year 2003 – 2006 probably due to submission by graduate students.

4.2 Characteristics of Protocol

4.2.1 Status of Principal Investigator

Majority of the principal investigators, 140/656 (67.1%) are postgraduate students while undergraduate students constitutes 11.6% (76/656). Postgraduate and undergraduate students constitute 78.7% while academic staff constitutes 21.3%. Details of the principal investigator status are shown in table 2 below:

Table 2: Status of Principal Investigator

Status	*N*	*%*
Student		
Undergraduate	76	11.6
Postgraduate	440	67.1
Staff		
Lecturer	24	3.7
Senior Lecturer	71	10.8
Associate Professor and Professor	45	6.8
Total	656	100

4.2.2 Sponsors of research

Most, 99% (512/516) of the studies submitted for review by students were funded from personal resources. None of the undergraduate research was funded while 2/440 of the graduate students protocols were funded by senate research grant and one (1/440) was part of an internationally funded study as shown in Table 3a. Of the 656 analyzed submissions, 85 (13.6%) were sponsored by funding agencies including international organizations

9.8% (65/656), university senate research grants 1.5% (10/656), pharmaceutical industries 1.7% (11/656) and other public institution in Nigeria 0.46% (3/656) (Table 3b).

Table 3a: Sources of funding

Status of applicant	Source of funding			
	Self	Donor	Not identified	Total
Student	512	3	1	516
Academic Staff	51	86	3	140
Total	563	89	4	656

Table 3b: Sources of funding

Cadre	Source of funding						Total
	1	2	3	4	5	6	
Undergraduate	76	-	-	-	-	-	76
Graduate	436	2	-	-	1	1	440
Lecturer	15	2	2		4	1	24
Senior Lecturer	30	6	8	1	24	2	71
Professor & Ass. Prof	6	-	1	2	36	-	45
Total	563	10	11	3	65	4	656

Key: 1=self funded, 2= senate research grant, 3=pharmaceutical company, 4=other public institution, 5= international, 6= not stated

4.2.3 Study sites

Six hundred and nine (92.8%) of the protocols were to be conducted in a single site while 47 (7.2%) were to take place in multi-sites. The research setting was a tertiary teaching hospital in 359 (54.7%) of cases; another 32 (4.9%) of protocols were conducted simultaneously in a tertiary teaching hospital and other health facilities. Other research location is as shown in Table 4.

Table 4: Location of study

Site	N	%
Tertiary Teaching Hospital (TTH)	359	54.7
TTH and others	32	4.9
Rural community	25	3.8
Urban community	117	17.8
Urban and rural community	9	1.4
Primary or Secondary health facility	15	2.2
University and other tertiary institution	72	11
Primary/Secondary schools	21	3.2
Specialized laboratory	3	0.5
Others	3	0.5
Total	656	100

The item "others" includes the prison, a beverage company and a conference venue

4.2.4 Nature of Research Protocols submitted to UI/UCH committee

Clinical researches constitute the bulk of the protocols submitted to the UI/UCH HREC accounting for 277 (44.9%) of research topic, this was followed by public health researches 122 (19.8%), laboratory based 119 (19.3%), 43 (6.9%) were on drug evaluation as shown in Table 5.

Table 5: Nature of Research protocols submitted to UI/UCH committee

Nature	N	%
Clinical	277	44.9
Public Health	122	19.8
Drug evaluation	43	6.9
Laboratory	119	19.3
Clinical and laboratory	30	4.8
Medical equipment	6	1
Social Science	11	1.8
Others	10	1.6
Total	618	100

4.3 Study Design and Scope of Research

The adopted design for the protocols was mainly descriptive in 76.2% (500/656), experimental, non-randomised in 12.8% and experimental randomised in 11%. Fifty percent (36/72) of the experimental randomised studies were conducted by senior academic staff (senior lecturer and above) and 40% (29/72) were conducted by postgraduate students as shown in Table 6. The proportion of experimental randomised studies varies from 21.4% (12/56) in 2002 to 5.1% (8/156) in 2004 as shown in Table 7. Studies were conducted mainly within the local setting in 83.3% of cases and nationally within Nigeria in 10% of cases while the proportion of international studies was 6.7%.

The number of international researches increased from 6 per year in 2002 to 11 per year in 2007 as shown in Table 8.

Table 6: Comparison of study design by principal investigator status

Cadre	Study Design			
	Descriptive	Experimental (non-randomised)	Experimental (randomised)	Total
Undergraduate	72	3	1	76
Postgraduate	353	58	29	440
Lecturer	15	3	6	24
Senior Lecturer	39	14	18	71
Professor & Assoc. Professor	21	6	18	45
Total	500	84	72	656

Table 7: Comparison of Study design by year of submission

Year of Submission	Study Design			
	Descriptive	Experimental (non-randomised)	Experimental (randomised)	Total
2002	27	17	12	56
2003	60	22	16	98
2004	132	16	8	156
2005	121	9	11	141
2006	91	3	10	104
2007	69	17	15	101
Total	500	84	72	656

Table 8: Comparison of scope of research by year of submission

Year of Submission	Scope of research				
	Local	National (single site)	National (multi-site)	International	Total
2002	34	2	4	6	56
2003	8	0	10	7	98
2004	138	2	14	2	156
2005	111	3	17	10	141
2006	90	0	6	8	104
2007	82	3	5	12	101
Total	546 (83.3%)	10 (1.5%)	56 (8.5%)	44 (6.7%)	656 (100%)

4.4 Expected duration of study

The expected duration of study was not specified in 201 (32.5%) of the protocol approved Over half (56.2%) of the protocol were expected to be conducted within a 12 months period as shown in Table 9 below.

Table 9: Expected duration of study

Expected duration of study	N	%
Within 3 months	134	21.7
>3 – 6months	121	19.6
>6 -12months	92	14.9
>12months	70	11.3

Table 11: Research Participants

Research Subject	N	%
Healthy Adults	197	31.9
Healthy children	22	3.6
Adult patient	270	43.7
Paediatric patient	51	8.2
Adult & paediatric patient	3	0.5
Adult patient & Healthy volunteers	10	1.6
Hospital records	56	9.1
Laboratory animals	2	0.3
Human corpses	2	0.3
Hospital facilities	5	0.8
Total	618	100

4.7 Incentive provided for research participants

Only 32 (5.3%, 32/618) approved protocols included explicit statements about the provisions of incentives for research participants in form of free medical assessments, free medication, payments for investigations, free snacks and soft drinks, stipend or re-imbursement of transport fare to the research site. Almost 60% (19/32) of the incentive were made available in self funded research while provision for incentive was stated in 20% (13/65) of funded research. Provision for incentive was stated in 3% (14/440) of graduate students' submission, and 12.9% (18/140) of academic staff submissions.

4.8 Revisions

Of the 618 approved protocols, 33 (5.3%) required no review before approval were provided while 464 (75.1%) required minor modifications after first review. One hundred and eighteen (19.1%) protocols required a second review while 3 (0.5%) required a third

review by the HREC. A revision could contain one or more points to be modified by the investigator. The average number of reasons for modification after review was approximately 2 per protocol approved. Donor-funded researches required less number of revisions as 71.9% (64/89) required one revision while 28.1% (25/89) required at least two revisions.

The main reasons for revision of submitted protocols before approval were inadequate information to the research participants as contained in the informed consent (283 protocols) inappropriate methodology and statistics (27 protocols), scientific factors (177 protocols), sample size calculation or justification (153 protocols), inclusion criteria (72 protocols), treatment information (62 protocols), study objectives not clearly stated (34 protocols), and legal requirements (e.g. NAFDAC number) (15 protocols). Other reasons include the need for a statement on confidentiality of data or participants (33 protocols), provision of incentives (4 protocols) and typographical errors (8 protocols).

Table 12: Reasons for revision before approval (n = 566)

Reasons	No of Protocols	%
Patient information on consent form	283	25.4
Methodology and statistics	271	24.3
Scientific justification	177	15.9
Sample size justification	153	13.7
Inclusion criteria	72	6.5
Treatment information	62	5.6
Study objectives	34	3.1
Legal requirements	15	1.4
Confidentiality	33	3.0
Typographical errors	8	0.7
Incentive	4	0.4
Total	1112*	100

*More than one reason per protocol reviewed

4.9 Approval

Six hundred and eighteen (618) protocols were approved during the study period while 38 protocols were closed after prolonged non-response from the principal investigators who were mainly undergraduate students. Of the approved protocols, 10 (1.6%) were exempt approval, 30 (4.9%) received expedited review while 12 (1.9%) received executive approval; the remaining 566 (91.6%) protocol required minor or major modifications before approval.

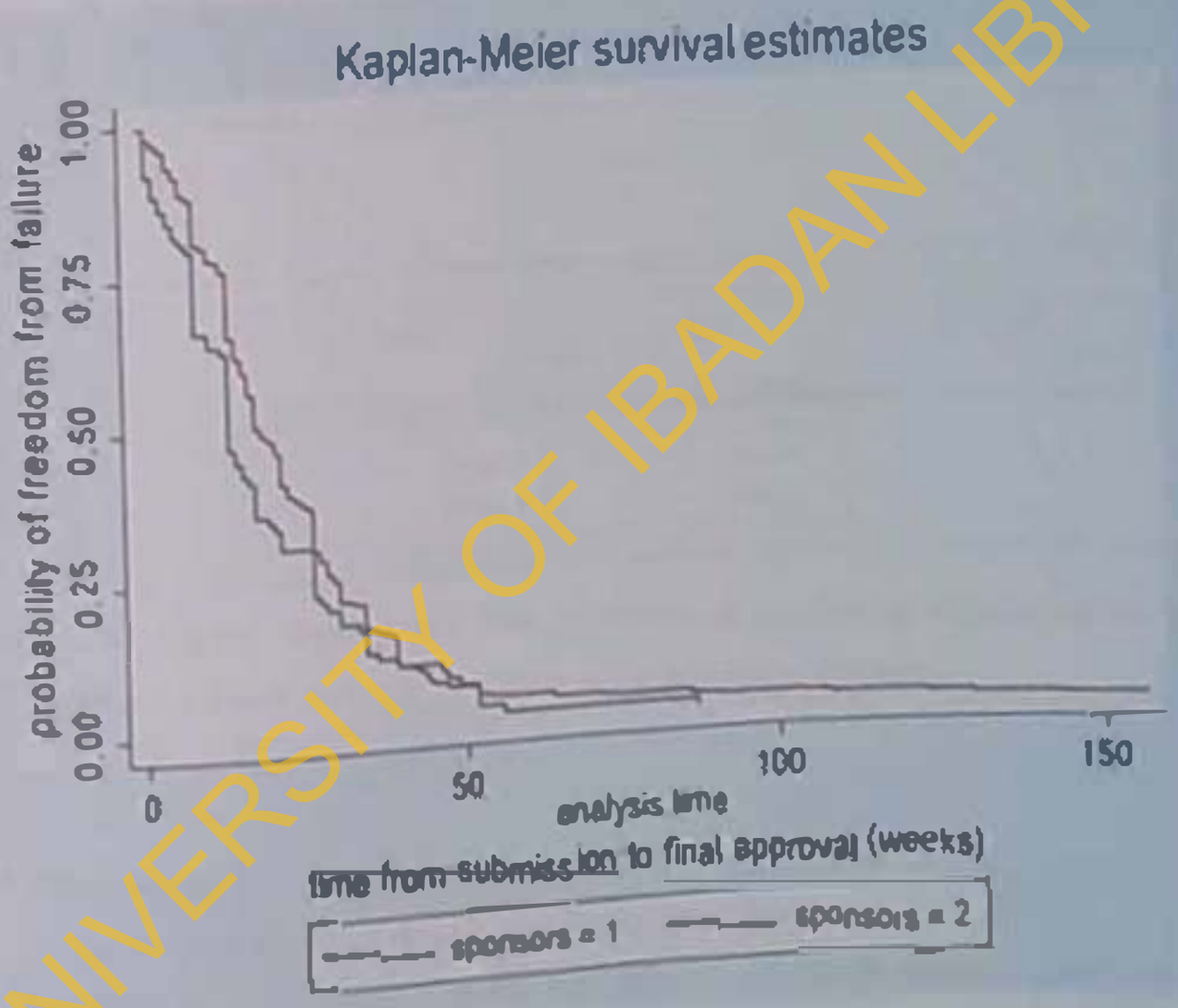
10 Duration of review

In general, the average time from submission to approval was approximately 21 weeks (95% CI: 20 - 23 weeks). It took a shorter time for protocols approved without further revision (n = 33, mean: 6weeks, 95%CI: 4 – 8 weeks) and internationally sponsored protocols (n = 64, mean: 16weeks, 95%CI: 12 - 20 weeks). The need for revision significantly affect the time taken from submission of research proposal to approval, $p < 0.001$ and also the number of revision required $p < 0.05$. The time taken for protocols requiring none, one or more revisions are shown in Table 13 below:

Table 13: Time from submission to approval

No of revisions	N	Mean (weeks)	Standard deviation	95% Confidence Interval	Range (weeks)
0	33	6.2	6.1	4.1 – 8.4	1 - 26
1	464	21.2	18.6	19.5 – 23	1 - 156
2	118	25.9	18.3	23 - 29	4 - 108
3	03	28.6	2.3	23 - 34	26 - 30

Figure: 1. KM graph showing the time from submission to approval for donor funded (sponsor=1) and self funded (sponsor=2) protocols. (Failure is defined as been approved)



Kaplan-Meier analysis indicates that type of funding and number of revisions required before approval are significant in determining the time from submission to approval. The hazard ratio for sponsored protocols on Kaplan-Meier analysis is 0.79, $p<0.05$ (figure 1) while the hazard ratio for number of revision required is 0.63, $p < 0.001$ (figure 2).

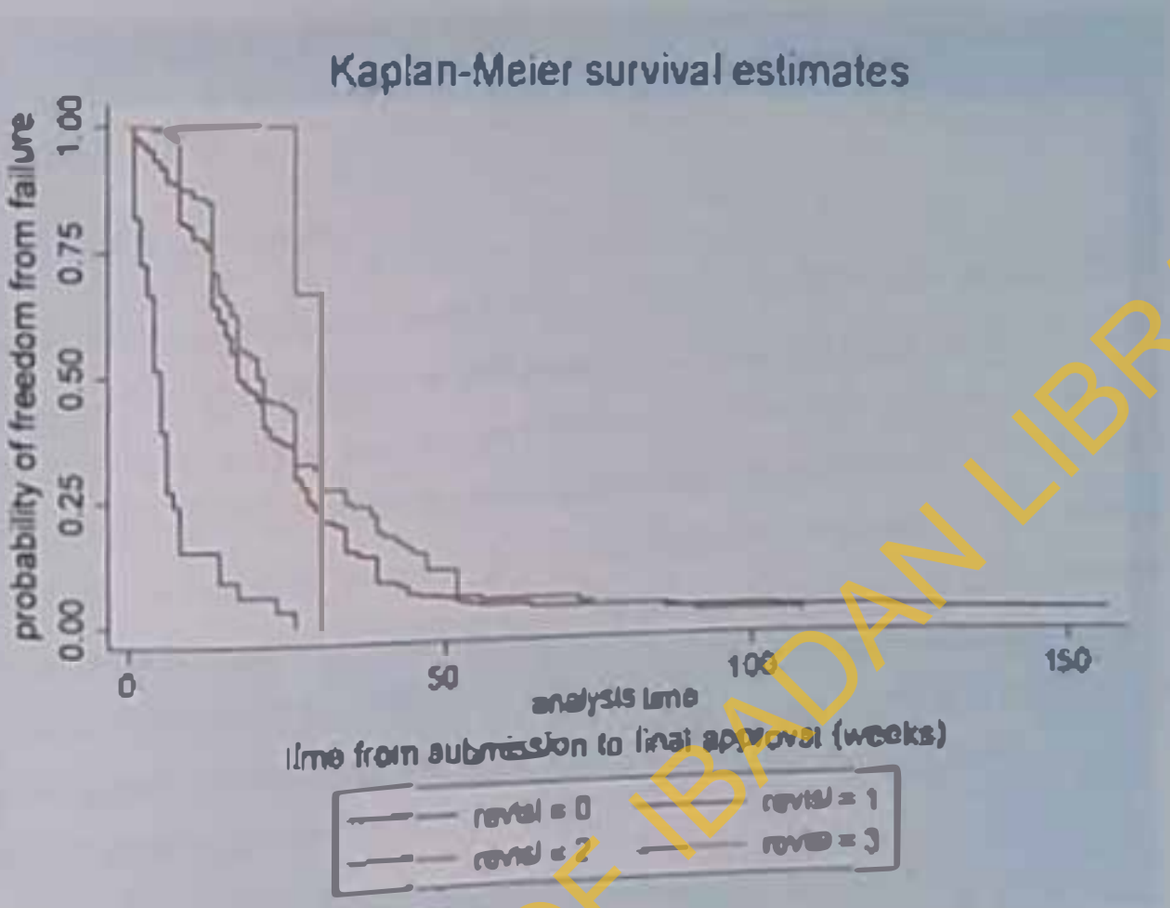


Figure 2: K-M graph showing time from submission to approval as regards number of revision required before approval. (revisi= Number of revision required)

4.11 Amendments (after approval)

Over 97% of the protocols approved required no further amendments after approval while 15 (2.6%) required further amendments in the sample size (3), incentives for participant and benefits to the community (5), adjustment or translation of the consent form (5), change in title (1) and one approval was withdrawn.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 DISCUSSION

Number of Protocol submitted

A total of 752 protocols were submitted to the UI/UCH HREC within the study period giving an average submission of 107 protocol per year and 9 protocols per month. Currently, for a protocol that requires a full review, a reviewer is given a two weeks period within which to review a protocol and submit comments to the UI/UCH HREC secretariat which then passes it on to the principal investigator. The principal investigator is required to respond to the reviewers' comment and make necessary modifications and or corrections. The reviewers' comment and the principal investigators' response are discussed by members of the UI/UCH HREC at their statutory meeting before approval or disapproval of the protocol is issued.

Status of Lead Investigators

Majority of the proposals reviewed by the UI/UCH HREC were submitted by graduate and undergraduate students (78.7%). The main reasons for this finding is that resident doctors are required to obtain the local HREC committee approval to do a research project in their final examinations leading to the award of fellowship by the West African College of Surgeons' or the National Postgraduate Medical College. Another reason that could account for the large numbers of proposals from students is the need to publish research findings in reputable international journals that would demand for the local HREC approval before publication of such.

Proposals from academic staff members constitute 21.3%. This indicated that academic staff sought approval for funded project while other research activities are not subjected to HREC review. Many staff members are reluctant to subject their study proposal for ethical review due to lack of understanding of the role of HREC in the research project (Ajuwon & Kass, 2008). There is therefore a need to provide

information and education on the role of HREC as an independent reviewer of a research proposal to prospective investigators and scientists. Other measures that could be employed to improve the current attitude of investigators at these institutions include the adoption of a policy that compels investigators at both institutions (UI/UCH) to submit their project for review before commencement. This policy should be empowered by the appropriate legal framework that would stipulate penalty for offenders. The UI/UCH HREC had taken a step towards achieving improved research ethics knowledge of prospective investigators by making procurement of a certificate of attendance from any of the internet based courses on research ethics a requirement for submission of protocol.

Sources of research funding

Over 80% (563/656) of the research were self-funded while 14.2% (93/656) received some funding from the university (senate research grant), pharmaceutical company or international donors. Internationally funded project account for 69.9% (65/93) of funded protocols approved in this study. Seeking international collaboration for research in Nigeria is a daunting challenge due to poor health infrastructure, lack of standard of care for many disease conditions and the prevailing poor economy and poverty in all ramifications. The CIOMS guideline states that "researchers working in developing countries have an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring country when possible" (CIOMS 1993). It is therefore, not surprising that international funded projects constitute <10% (65/656) of the total protocols analyzed in this study. It is almost impossible to meet sponsoring country standard of care as specified in CIOMS guideline in many instances in developing countries.

Study design, nature of research and sample size

The term "design" encompasses all structural aspects of a study including the definition of the study sample, size of sample, method of treatment allocation, type of

statistical design (randomised, cross-over, others), and the choice of outcome measures (Altman, 1980). The definitions suggest that in reviewing the research protocol, the ethics committee should determine the knowledge claims being made by the researcher in the background to the study, the strategies of inquiry (experiment or survey), method of data collection and analysis that will be used. In this study, many research protocols submitted were on clinical (277/618, 44.9%) and public health (122/618, 19.8%) studies; hence the ethics review often examine the characteristics of the study sample based on the inclusion and exclusion criteria. Inappropriate methodology was a major reason for re-review of many of the submitted protocols (271/1112, 24.3%) suggesting that most lead investigators (mainly students) did not understand this aspect of study protocols.

The ethics committee must ensure that the study sample is as representative of the population as possible in order to allow for generalization of the results, however for many population in the clinical setting where no sampling frame may exists, it is often difficult to obtain a representative sample. In this review, many, (500/656, 76.2%) protocols were of survey design defined here as being descriptive study employing questionnaire or clinical interviews to generate data. Included in the descriptive design are the 11 (11/618, 1.8%) social science studies which were mainly ethnographies and case studies. In ethnographies, the researcher studies an intact cultural group in a natural setting over a prolonged period of time by collecting observational data while case studies explored in depth a program, an event, an activity or a process of one or more individuals (Creswell, 2002). Observational studies are often deemed non-invasive, however, such studies may involve visiting people at home, expecting them to complete and return a questionnaire, or to attend a clinic, thus may be liable to non-cooperation or poor response rate. Therefore, the ethics committee must ensure that the questionnaire is short and simple or few clinic attendances are necessary to help reduce the non-response rate.

Sample size calculation is of utmost importance in Randomized controlled Clinical Trial (RCT) because it is unethical to enrol more subjects than are needed to

answer a researcher question because unwarranted numbers needlessly expose subjects to the risks of research. Conversely, if too few subjects are enrolled in a study, that design is unlikely to answer the research question (Leon, 2008). In this analysis experimental randomised studies constituted only 11% (72/656) of the protocols submitted for review and fifty percent (36/72) of the experimental randomised studies were carried out by senior academic staff (senior lecturer and above) and 40% (29/72) were carried out by postgraduate students. This finding suggests that only senior academic staff or postgraduate students who are under supervision of such staff are able to perform this type or research. However, many of the protocols classified as randomised studies in this analysis were not strictly a RCT but studies comparing the effects of known standard treatments or interventions. Errors in sample size justification are responsible for the return of over a quarter (153/566, 27%) of the submitted protocols to principal investigator for correction.

Sample size is determined using statistical power analyses method which include setting the type I error (typically set at 0.5), the statistical power (usually set at 0.8) and the research design (data analysis methods). Type I error is the probability of rejecting the null hypothesis (For instance the probability that a drug is an effective pain reliever) when it is otherwise true (Rosner, 2006). There are many formulae for calculating the power of a study depending on the type of study sample required (one sample or two sample study), sample characteristics and the type of data. As noted earlier sample size determination, methodology and statistics are major deficient area for many researchers as shown in this study; hence efforts should be directed at improving knowledge in this area.

Duration

A significant number of the protocols submitted were of short duration (130/618, 21.7%) indicating that there is a need to complete studies within a short period. The reason for this observation is not unconnected with the fact that majority of lead

investigators are postgraduate students who needed to complete and submit dissertation within a stipulated time in order to qualify for sitting the final examinations. Generally, very few studies are conducted for more than one year (70/618, 11.3%) which shows that only few longitudinal studies are being conducted in the two institutions that host the ethics committee. Longitudinal studies are difficult to perform due to a high attrition rate, financial commitments and human resources required.

Study sites and research participants

Studies were mainly hospital based with over 54.7% (359/656) being conducted in a tertiary hospital while 23% (151/656) were community based. These findings simply affirmed the fact that graduate students constitute the bulk of the investigators and it is probably easier to conduct studies in hospital settings because of ready access to hospital patients. The use of hospital patients (324/618, 52.4% in this study) as research participants raises valid ethical and moral issues because doctors may find their obligation as health care providers to individual patient come into conflict when they become investigators. To avoid exploitation of hospital patients and undue influence, strict adherence to the 3 principles guiding ethical conduct of research must be ensured. Respect for person underlies the duty of the doctor to obtain informed consent from study participants; beneficence demands a favourable balance between the potential benefits and harms of participation; justice requires that vulnerable people are not exploited and eligible candidate who may benefit from participation are not excluded without a good cause (Weijer et al 1997). Moreover, the study must be designed in a way that ensures the validity of findings, and address questions of sufficient importance to justify the risks of participation. However, in this study, the study designs were mainly descriptive (76.8%, 474/618).

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Incentive provided for research participants

It is often difficult to carry out research without willing participants who would give voluntary consent; therefore providing incentives may be perceived as a means to motivate participation of human subject in researches. In this study, incentive was made available in 5.3% (32/618) of the protocol reviewed. The incentives offered varied from free medical assessments, free snacks and soft drinks to reimbursement of transport fare or stipend to research participants. There is a controversy on monetary incentive to study participants, while some authors argued that paying subjects is unethical, others agree that it is acceptable in some cases (McNeil, 1997, Ackerman, 1989 & McGee, 1997). The major ethical concern is that monetary incentives may constitute an undue influence to induce subjects to participate in research by compromising the voluntary nature of their decision to participate (Macklin, 1981).

Payment of study participants should be considered carefully during the review process particularly in Nigeria where many people live below the poverty line and good health care is hard to come by. In a study by Dicken and colleague on 32 organizations involved in the development, conduct and review of biomedical research (9 academic centres, 7 pharmaceutical companies, 8 contract research organizations and 8 independent institutional review boards (IRBs) based in the United States of America), 37.5% had written guidelines on payment of research subjects while only 18.8% were able to provide an estimates of the proportion of studies that pay subjects (Dicken et al 2002). Payment is usually made to compensate for participants' time, inconvenience, travel or incurring risk. There is a need to establish a standard policy at the UI/UCH HREC to guide the use of monetary incentive to study participants in order to safeguard the use of money as a means of coercion or undue influence to participate in research.

Reasons for revision

Information provided on the informed consent document remains one of the major reasons for revision of protocols as found in this study (50%, 283/566) and other

similar studies, 46% (Deculier and colleague, 2005) and 85% (Boyce, 2002). In order to be ethical, an informed consent must be obtained from human participants according to the Declaration of Helsinki which states

" in any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and discomfort it may entail" (Declaration of Helsinki, 1964).

The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed. It is often difficult for most researchers to capture the details of the requirement as stated in the Helsinki's declaration on their informed consent form as shown in this study. The UI/UCH HREC has made a prototype- informed consent document that contains all the information required in the Helsinki's declaration in order to simplify this aspect for prospective investigators.

Modifications of research protocol before approval

A major finding in this study is that over 75% (464/618) required modifications before approval compared to 51% reported by Decullier and colleague (Decullier et al 2005). The need for revision and number of times a protocol is reviewed significantly affect the time from submission of research proposal to approval. As noted by Ahmed and Nicholson in their study involving multi-centre studies, delay in obtaining approval from local IRECrelate to the frequency with which ethics committees meet, and also their workload (Ahmed & Nicholson, 1996). The UI/UCH HREC meets once a month to review the protocols submitted for review, unfortunately, the limitation of this study is that HREC workload was not determined. However, the time taken from submission to approval can be improved through training of researchers, trainees and

other staff cadre in Good Clinical Practice, research ethics, study design and research methodology. This training should be made available locally and affordable to the undergraduate and graduate students that constitutes the bulk of investigators patronizing the UI/UCH HREC.

Time from submission to approval

In this study, it takes an average of 21weeks for a protocol to pass through the full review process; this is contrary to the NHREC (section E (d) (5)) guideline which stipulates a maximum period of 3 months from the date of receipt of a valid application. HREC review appears to take longer time at the UI/UCH HREC when compared to other findings from other countries. For example, Dal-Re and colleagues discovered that it takes 64 days from submission to approval of protocol in Spain while it takes a mean of 27days in France (Dal-Re et al 1999). Approval for internationally funded research protocols took a shorter period (16weeks) compared to self-funded researches (21 weeks). The probable reasons for this observation include the fact that internationally funded protocols are better-written, are conducted by senior members of staff who respond more quickly to reviewers' comment because of tight deadlines and fear of losing the grant.

Delay in review of proposals by the local HREC is a common problem that had been identified by many researchers. The main cause of delay in the full review process is the need for a full review by appointed reviewer and the entire member of the HREC. Other sources of delay in review by the UI/UCH HREC include inefficient mailing of submitted proposals to reviewers, delay in receipt of reviewers' comments', investigators slow response to corrections and inability to review protocols by HREC members within the stipulated time (2 weeks) due to other commitments (Falusi et al 2007).

5.2 CONCLUSION

The UI/UCH Health Research Ethics Committee which provides a platform for review of research to be carried out in the sister institutions had been in existence since the early 1980's (Falusi, 2004). The Ethics committee was granted a Federal Wide Assurance number FWA0003094-U in May 2002 by the American Office for Human Research Protection (OHRP) and was registered with the National Health Research Ethics Committee (NHREC) in 2007.

An audit of the protocol submitted to the UI/UCH HREC in the years 2002 to 2007 was performed between August and October 2008. The objectives of the study are to: document the number of submission received during each year of review, describe the types of proposals submitted to the HREC, the process of review with respect to duration of each review and the profile of investigators who had submitted proposals during the period under consideration.

It was noted that the UI/UCH HREC meets once a month to review the protocols submitted for review and has a dedicated secretariat staffed with appropriately trained staff, clear guidelines on submission process and a prototype informed consent document that aid prospective investigators.

The HREC reviews and gives approvals in compliance with international codes of ethics, the declaration of Helsinki, CIOMS, and the NHREC guideline. All research protocols involving human participants including the use of human specimens, tissues, embryos, foetal materials or surveys.

Since the inception of the UI/UCH HREC in 2002, two guidelines have emanated from the committee and one published report titled "Establishment

of a standing ethics/institutional review board in a Nigerian University: A lifetime for developing countries? Falusi and colleagues noted that over a 3year period following the establishment of the IRUCH HREC, 500 application were received and the average period between protocol submission and approval decreased from 7.87months in 2002, to 3.69months in 2005 (Falusi et al 2007).

Following the HREC approval, a retrospective review of each of the protocols received between 2002-2007 were reviewed and relevant information extracted by the candidate using a 25-item questionnaire. The results showed that the committee received a total of 732 protocols, 618 were approved while 38 protocols were closed after prolonged non-response from the principal investigators. Majority of the protocols were submitted by students (78.7%) while academic staff constitutes 21.3%. Of the 656 submissions analyzed, 89 (13.6%) were sponsored by funding agencies while clinical research on human participants constitute the bulk of the protocol submitted accounting for 44.9% of research topic. Thirty-three protocols were granted exempt approval and 464 required only minor modifications after first review. The average time from submission to approval is approximately 21 weeks. Findings in this study indicate that there is a need to improve on the review process in order to reduce delays.

In conclusion, the time taken from submission to approval can be improved through training of researchers, trainees and other staff cadre in research ethics, study design and research methodology and statistics. This training should be made available locally and affordable to the body of undergraduate and postgraduate students that constitutes the bulk of investigators patronizing the UI/UCH HREC.

5.2 Recommendations

1. Increase the number of trained reviewers and expertise available for consultation by encouraging members of staff to attend seminars and workshops on research ethics
2. Research grants should be provided by UI and UCH management to fund postgraduate studies in order to ensure that scientifically sound and ethically justified researches with good study design and methodology are conducted
3. Increase public-private partnership in research funding through collaboration with industries and pharmaceutical companies
4. Training in research ethics, study design, research methodology and statistics for academic staff and students

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Appendix I

Data Retrieval Form

Protocol identification number..... Month of submission.....

Year of submission:.....

1. Principal Investigator status

i] Undergraduate student
ii] Postgraduate students –Resident doctor
iii] Postgraduate students-(MSc, PhD, Fellowships specify)
iv] Assistant Lecturer
v] Lecturer II
vi] Lecturer I
vii] Senior Lecturer
viii] Associate Professor
ix] Professor

2. Type of sponsor

i] Personal
ii] University (Senate Research Grant)
iii] Tertiary Teaching Hospital
iv] Industry
v] Pharmaceutical company
vi] Other public institutions in Nigeria (specify)
vii] International Organization
viii] Non-governmental organization (Local / International, specify)

3. Location of Research

i] Rural community
ii] Urban community
iii] Health facility (Primary, Secondary, tertiary, specify)
iv] Primary/ Secondary schools
v] Higher institution /University community
vi] Specialized Laboratory
vii] Others (specify)

4. Type of research

i] Drug: Phase I / Phase II / Phase III
ii] Cosmetic and Nutrition
iii] Physiological
iv] Clinical diagnostic
V] Laboratory diagnostic
vi] Medical equipments and prosthesis

Appendix I

Data Retrieval Form

Protocol identification number..... Month of submission.....

Year of submission:.....

1. Principal Investigator status

i] Undergraduate student
ii] Postgraduate students –Resident doctor
iii] Postgraduate students-(MSc, PhD, Fellowships specify)
iv] Assistant Lecturer
v] Lecturer II
vi] Lecturer I
vii] Senior Lecturer
viii] Associate Professor
ix] Professor

2. Type of sponsor

i] Personal
ii] University (Senate Research Grant)
iii] Tertiary Teaching Hospital
iv] Industry
v] Pharmaceutical company
vi] Other public insitutions in Nigeria (specify)
vii] International Organization
viii] Non-governmental organization (Local / International. specify)

3. Location of Research

i] Rural community
ii] Urban community
iii] Health facility (Primary, Secondary, tertiary, specify)
iv] Primary / Secondary schools
v] Higher institution /University community
vi] Specialised Laboratory
vii] Others (specify)

4. Type of research

i] Drug: Phase I / Phase II / Phase III
ii] Cosmetic and Nutrition
iii] Physiological
iv] Clinical diagnostic
V] Laboratory diagnostic
vi] Medical equipments and prosthesis

vii] Surgical

viii] Public Health
ix] Social Science
x] Others (specify)

5. Study Design
i] Descriptive, analytic
ii] Experimental, non-randomized
iii] Experimental randomized

6. Scope of research
i] Local
ii] National –monocentric
iii] National – multicentric
iv] International
v] Not available

7. Expected Sample size .....

8. Expected duration of study .....
9. Benefits to study participants
i] No direct benefit
ii] Direct benefit
iii] Incentive / Compensation (specify type)
iv] No incentive
v] Not available

10. Characteristics of study participants
i] Residents in a community
ii] School children (Primary/secondary)
iii] University/ other tertiary institution students
vi] School teachers / university staff
v] Paediatric patients
vi] Adult hospital patients
vii] Health volunteers
viii] Others (specify)

11. Number of revisions before approval .....

12. Reasons for revisions (this list is not exhaustive)
i] Patient information
ii] Inclusion / Exclusion criteria
iii] Scientific prerequisite
iv] Legal and administrative requirements

v] Sample size
vi] Information on treatments and examination
vii] Study objectives
viii] Information on methodology and statistics
ix] Others (specify)

13. Time from submission of application to approval.....

14. Reasons for delay in approval
i] Principal investigators factor
ii] Required many amendments/ revision
iii]Sponsor factor
vi] Research ethic committee factor
v] Others – specify

15. Number of amendments after approval.....

16. Reasons for amendments
i] Change in sample size
ii] Modification of inclusion criteria
iii] Modification of the timetable
iv] Changes in examinations and treatments
v] Others (specify)

17. Disapproval of protocol
i] Reasons clearly stated
ii] Reasons not clearly stated
iii] No reasons stated
iv] Investigator's response
v] No investigator response

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UI/UCH HREC Registration Number: NHREC/05/01/2008a
Date: 07/07/2008

NOTICE OF EXPEDITED APPROVAL

Re: Audit of Protocol Submissions to the University of Ibadan/University College Hospital Health Research Ethics Committee (2002 – 2007).

UI/UCH Health Research Ethics Committee assigned number: UIEC/08/0030

Name of Principal Investigator: Dr. Olayinka R. Fyelade

Address of Principal Investigator: Department of Anaesthesia,
College of Medicine,
University of Ibadan, Ibadan

Date of receipt of valid application: 04/07/2008

Date of meeting when final determination of research was made: N/A

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and given exempt approval by the *UI/UCH Health Research Ethics Committee*.

This approval dates from 07/07/2008 to 06/07/2009. If there is delay in starting the research, please inform the UI/UCH Health Research Ethics Committee so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the UI/UCH HREC assigned number and duration of UI/UCH HREC approval of the study.* In multiyear research, endeavour to submit your annual report to the UI/UCH HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the UI/UCH HREC. No changes are permitted in the research without prior approval by the UI/UCH HREC except in circumstances outlined in the Code. The UI/UCH HREC reserves the right to conduct compliance visit to your research site without previous notification.

UI/UCH IRB
APPROVED
07/07/2008
COLLEGE OF MEDICINE U.I.

Prof. C. A. Adebamowo
Chairman, UI/UCH HREC
E-mail: uichrec@yahoo.com