Ethics in Clinical Research

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Picture this scenario

The "standard" Jehovah's Witness Case

- A competent adult patient loses a massive amount of blood from a bleeding acute duodenal ulcer. The best chance of saving his life is an urgent blood transfusion along with operative intervention to arrest the bleeding. The patient refuses blood but asks for treatment instead with the best available non-blood products, and surgery, accepting the substantial risk that surgery without blood transfusion is much less likely to save his life than surgery with blood transfusion.

Scenario 2

THE "STANDARD" CHILD OF A JEHOVAH'S WITNESS CASE

- A 2 year old child has lost a massive amount of blood in a road accident and again the best chance of saving the child's life is an urgent blood transfusion and operative intervention to arrest the bleeding. Both the child's parents are Jehovah's Witnesses and refuse to give permission for a blood transfusion, requesting instead that the best available non-blood products are used to restore volume and that surgery is carried out without blood. They understand that this will be a far more dangerous course of action than surgery plus blood transfusion but persist in refusing permission for a blood transfusion for their child.

Scenario 3

SELLING KIDNEYS FOR TRANSPLANTATION

Should people be allowed to sell a kidney for transplantation?

Why ethics is important

- Nowadays, conflicts of interests between
  - Government and medical institutions
  - Between medical institutions and medical personnel
  - Between physicians and patients
- High technologies not only brought us hopes of cure but have also created a heavy economic burden.
- The ethical dilemmas of high technology medicine-brain death, organ transplantation, and concerns about quality of life-have become increasingly prominent.
- Multi institutional, multinational research

- The three previous scenarios illustrates the issues facing ethics
- Ethics is nothing more than a system of principles or values which can help us in decision-making.
- It is not necessarily about discovering what is right.
- In medicine there are often contrasting views that have their own legitimate morality (morality = a personal, intuitive sense of what is right or wrong).
- This is when ethics is required. When used to decide these issues, ethics has to justify the path taken.

What is Biomedical Ethics?

- Ethics is a philosophical consideration of morals: right or wrong
- It is a process of thinking, of morals, of behaviour and intentions
- Ethics evolves out of a collective responsibility to humanity
- The term "bio-medical ethics" was coined in the early 1970s to refer to the application of moral reasoning to vexing questions at the frontiers of biology and medicine

Ethics is not:

- Merely obeying the law:
  - Compliance

Although in many instances laws are statements of considered ethical positions and most of the time obeying the law is an element of ethical behavior.

What constitutes a Research?

- Sometimes it can be difficult to distinguish research from program evaluation, health care or public health interventions
- If the goal is "generalizable knowledge", then the activity is research
- If the goal is to generate knowledge relevant only to a particular individual or program, then it is not

What constitutes a Research? Cont'd

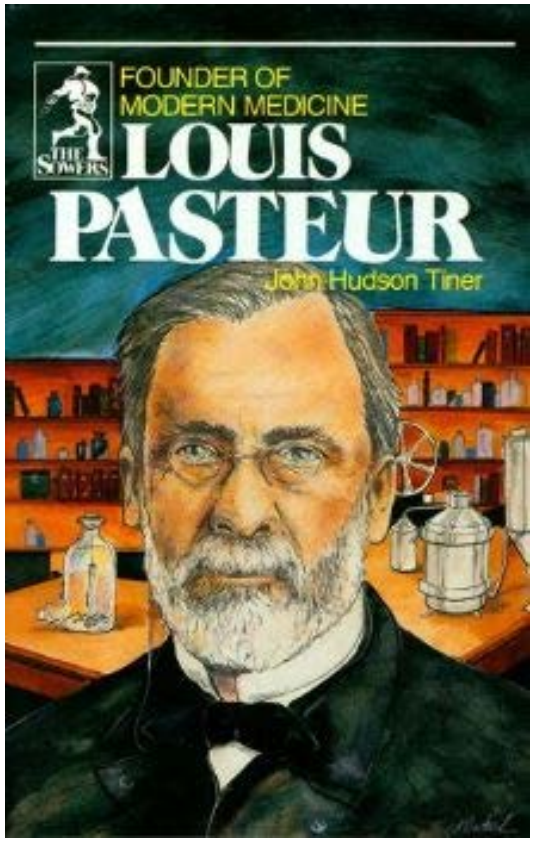
- All healthy research must be scientifically sound to be ethical
- The scientific merit of any research must be matched with the ethical process
- Unsound research on human subjects may expose research subjects to risks or inconvenience.

The Evolution of Research Ethics

The Evolution of Research Guidelines

PRE- 20TH CENTURY EXPERIENCE

- Before the 20th century, many "clinical trials" were small in scale and therapeutic in intent.
- These included the:
  - Smallpox vaccination trials of Edward Jenner
  - The rabies vaccination trials of Louis Pasteur.



The Evolution of Research Guidelines

BEFORE WORLD WAR II (1919-39)

- Start of a new era of research that contrasted with the small scale experiments carried out previously.
- Many experiments were carried out in state institutions (using the poor, orphans, mentally ill).
- Such populations represented a captive and compliant group of people who "seemed ideal" for experimentation.
- Experiments involved, for example, exposing subjects to gonorrhea and syphilis.
- In many cases, the subjects had no knowledge they were taking part in research.

The Evolution of Research Guidelines

- More significantly, all of these activities that went on prior to World War II were done in the absence of formal codes or regulations to guide the ethics of the conduct of clinical research.
- What brought about the regulations?

The Evolution of Research Ethics

- Ethical review and bio-medical ethics evolved in response to a history of medical abuses
  - Medical abuses by Nazi doctors (Nuremburg Trial and code of 1947)
  - Public revelation of the Tuskegee syphilis study in 1974

NAZI WAR CRIMES-WORLD WAR II

- During World War II, Nazi doctors performed horrific experiments on thousands of concentration camp inmates.
- These included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.

THE NUREMBERG TRIAL

- The trial was held in Nuremberg, Germany, from December 9, 1946, to August 20, 1947.
- 23 medical personnel were accused of inhuman experimentation and euthanasia

The lesson of Nuremberg trials

"No trial provides a better basis for understanding the nature and causes of evil than do the Nuremberg trials from 1945 to 1949. Those who come to the trials expecting to find sadistic monsters were generally disappointed.

What is shocking about Nuremberg is the ordinariness of the defendants: men who may be good fathers, kind to animals, even unassuming--yet committed unspeakable crimes.

Years later, reporting on the trial of Adolf Eichmann, Hannah Arendt wrote of "the banality of evil." Like Eichmann, most Nuremberg defendants never aspired to be villains. Rather, they either over-identified with an ideological cause or suffered from a lack of imagination: they couldn't fully appreciate the human consequences of their career-motivated decisions"

Nuremberg Code (1947)

- Based on the aftermath of the doctors' trial at Nuremberg
- Consists of 10 principles or points

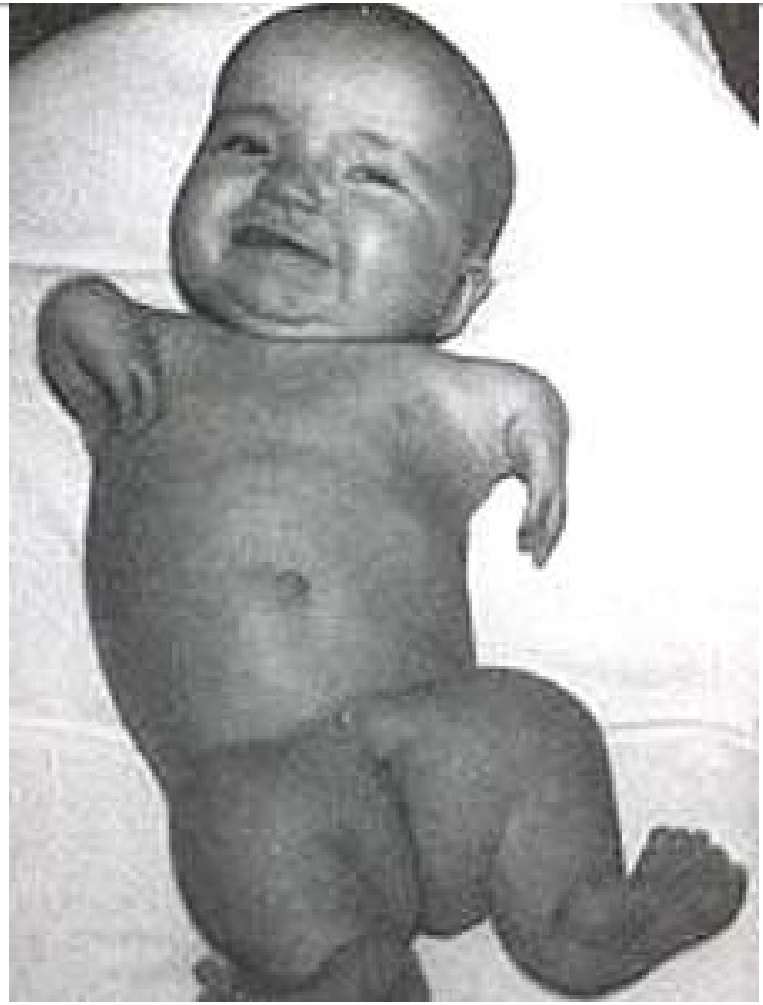
1. Voluntary human consent is essential
2. Experimental results should results in good for society
3. Anticipated results should justify the experiment
4. Avoid all unnecessary physical and mental suffering
5. No experiment if there is a chance of death/disability
6. Minimize risk of subjects
7. Proper preparations and facilities to protect subjects
8. Experiments conducted only by qualified persons
9. Subjects can withdraw at anytime
10. Terminate experiment if results are known or with best judgement

Despite the Nuremberg Code, unethical experimentations were still common…..

We will look at two examples

(1) THALIDOMIDE

- In the 1950s, thalidomide was approved as a sedative in Europe; **it was *not* approved in the United States by the FDA.**
- To control sleep and nausea throughout pregnancy.
- It was soon found that taking this drug during pregnancy caused severe deformities in the fetus
- Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent.
- Some 12,000 babies were born with severe deformities due to thalidomide.
- "one of the biggest medical tragedies of modern times"



THALIDOMIDE (2)

- The U.S. Senate hearings followed
- In 1962 the so-called "**Kefauver Harris Amendments**" to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety.
- For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them.

(2) THE TUSKEGEE SYPHILIS STUDY

- The research project was conducted by the U.S. Public Health Service from 1932-72.
- Six hundred low-income African-American males, 400 of whom were infected with syphilis, were monitored for 40 years.
- Free medical examinations were given; however, subjects were not told about their disease.
- Even though a proven cure (penicillin) became available in the 1950s, the study continued until 1972 with participants being denied treatment.

THE 1932-72 TUSKEGEE SYPHILIS STUDY

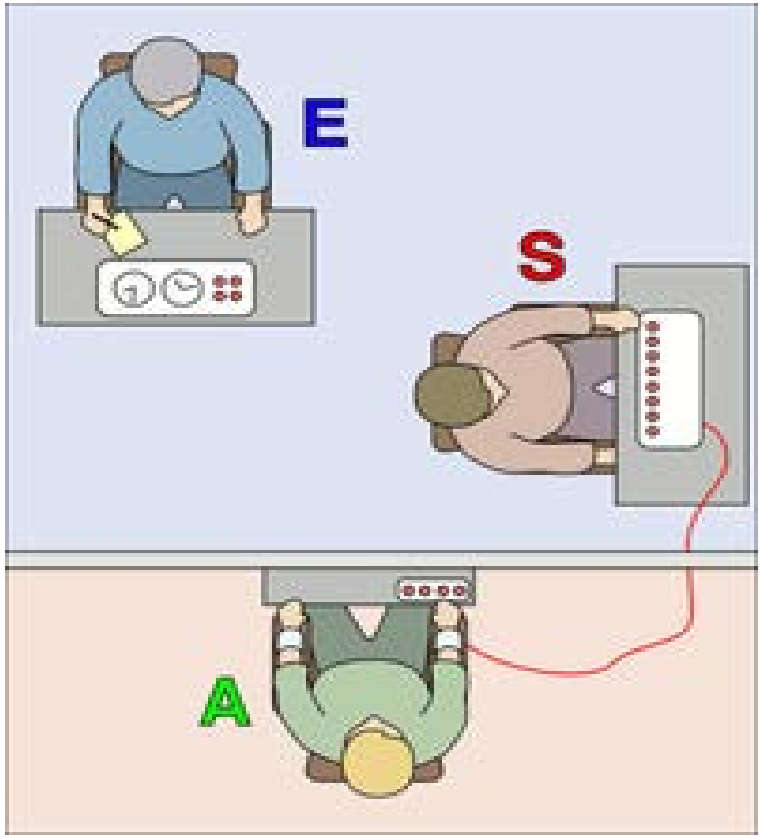
- In some cases, when subjects were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment.
- The victims of the study included numerous men who died of syphilis, wives who contracted the disease, and children born with congenital syphilis
- The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment.
- "arguably the most infamous biomedical research study in U.S. history,"
- In 1997, under mounting pressure, President Clinton apologized to the study subjects and their families.

Why did these horrific things happen?

- Could it be that Nazi war criminals and their million accomplices in the Holocaust were just following orders?

- How easily can ordinary people be influenced into committing atrocities as by Nazis in WWII.

1963: Milgram Experiment: Will people do anything ordered?



- The experimenter (E) orders the subject (S) to give what the subject believes are painful electric shocks to another subject (A), who is actually an actor.
- Many participants continued to "give" shocks despite pleas for mercy from the actor, as long as the experimenter kept on ordering them to do so.

1964: The Declaration of Helsinki (1)

- The WMA initiated its own research ethics guidelines in 1953….Took several years
- In 1964, the WMA established recommendations guiding medical doctors in biomedical research involving human subjects.
- The Declaration
  - Governs international research ethics
  - Defines rules for "research combined with clinical care" and "non-therapeutic research."
  - Was revised in 1975, 1983, 1989 and 1996 and is the basis for Good Clinical Practices used today.

1964: The Declaration of Helsinki (2)

Issues addressed in the Declaration of Helsinki include:

i. Research with humans should be based on the results from laboratory and animal experimentation
ii. Research protocols should be reviewed by an independent committee prior to initiation
iii. Informed consent from research participants is necessary
iv. Research should be conducted by medically/scientifically qualified individuals
v. Risks should not exceed benefits

http://www.wma.net/en/30publications/10policies/b3/

1974: The National Research Act (USA)

- Was passed due to the publicity from the Tuskegee Syphilis Study.
- The Act created the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**, which was charged to
  i. identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and
  ii. to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.
- The Commission drafted the **Belmont Report**, a foundational document in for the ethics of human subjects research in the United States.

1979: THE BELMONT REPORT

- Prepared by the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**
- It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

Belmont Report

Guided by Four Principles

1. **Respect for Persons**
    1. Autonomy
    2. Those with diminished capacity/status deserve protection
2. **Beneficence**
    1. Act in best interest of patient
3. **Non-maleficence**
    1. Do no harm
    2. Maximize benefits/minimize harm (double effect)
4. **Justice**
    1. Giving every person her or his due: equality of justice
    2. Injustice occurs when a person entitled to a benefit is denied it without sufficient reason or when an undue burden is imposed.

Principles become expressed in policies and practices

1. Informed Consent
    1. Information
    2. Comprehension/understanding
    3. Voluntary
2. Privacy/Confidentiality
3. Refusal to allow one individual make complex decisions about treatment/care
4. Ethics committees
5. Ethics consults

Ethical Principles

- **Zeke Emmanuel 10 ethical principles:**
  i. scientific value
  ii. scientific validity
  iii. fair selection of participants
  iv. minimization of risk and maximization of benefits
  v. independent review
  vi. informed consent
  vii. respect for persons
  viii. trust relationship
  ix. protection
  x. justice

Ethical Principles

- **Scientific value.**
  - Every research study is designed to answer a specific question.
  - Answering certain questions should have significant value for society or for present or future patients with a particular illness.
  - An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others.
  - In other words, answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease.

Ethical Principles

- **Scientific validity.**
  - A study should be designed in a way that will get an understandable answer to the valuable research question.
  - This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices.
  - It is also important that statistical plans be of sufficient power to definitively test the objective, for example, and for data analysis.
  - Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose.

Ethical Principles

- **Fair subject selection.**
  - Who does the study need to include to answer the question it is asking?
  - The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study.,
  - People should be chosen in a way that minimizes risks and enhances benefits to individuals and society.
  - Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens.
  - Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk.

Ethical Principles

- **Minimization of risk and maximization of benefits**
  - Also called "**Favorable risk-benefit ratio**"
  - Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research.
  - And by definition, there is more uncertainty about risks and benefits in early-phase research than in later research.
  - Has everything been done to minimize the risks and inconvenience to research subjects, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks?
  - Research volunteers often receive some health services and benefits in the course of participating, yet the purpose of clinical research is not to provide health services.

Ethical Principles

- **Independent review.**
  - To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts
  - Review panel must have no vested interest in the particular study should review the proposal and ask important questions, including:
    - Are those conducting the trial sufficiently free of bias?
    - Is the study doing all it can to protect research volunteers?
    - Has the trial been ethically designed and is the risk–benefit ratio favorable?
  - Should also monitor a study while it is ongoing.

Ethical Principles

- **Informed consent.**
  - For research to be ethical, individuals should make their own decision about whether they want to participate or continue participating in research.
  - It is a process by which individuals:
    i. are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research,
    ii. understand this information and how it relates to their own clinical situation or interests, and
    iii. make a voluntary decision about whether to participate.

Ethical Principles

- **Respect for potential and enrolled subjects.**
  i. Respect their privacy and keep their private information confidential.
  ii. Respect their right to change their mind
  iii. Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.
  iv. Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.
  v. Informing them about what was learned from the research. Most researchers do a good job of monitoring the volunteers' welfare and making sure they are okay. They are not always so good about distributing the study results.

What Ethics Committees (Should) Do

- **Gather Relevant Data, t**hrough:
  - Reading of proposals and other relevant documents
- **Identify Values and Principles Implicated in Case**
  - e.g. autonomy, informed consent, confidentiality, etc.)
- **Identify Related Normative Issues**
  - Social norms
  - laws
  - institutional policies
- **Identify and analyze Range of Morally Acceptable Options for the Case**
- **Building Agreement on Act to extent Possible**
  - Ensure that researchers take steps to make sure that involved parties have their voices heard (patients, families, surrogates, health care providers)
  - Help facilitate (to extent possible) building of morally acceptable shared commitments or understandings within the context

Evaluating a Study

- Does the study ask an important/valuable question?
- Is the study design reasonable?

- Would I be willing to be in this trial?

Evaluating a Potential Volunteer

- Level of understanding based on
  - Education, life experience
- Motivation
- Financial need
  - vs. ethics of lack of universal health care
  - What will happen to the pt when the study ends?
- Stage of illness
  - Risk vs. Benefit
  - What do they have to lose?
- Would I take this drug or give it to my family member?

LAUTECH Ethical Committee: A Brief History

- Inaugurated on Tuesday, August 15 2006
- By the then CMD of the hospital, Prof Kola Obisesan
- To fulfil the perceived need of the hospital for a functional ethical committee.

Inaugural Members

- Dr Oluwadiya Kehinde Sunday.
- Miss. Ndukwe Yvonne U.
- Dr. Oparinde Dolapo P.
- Mr. Muhibi Musa A.
- Dr. Adeniji Oladeni A.
- Dr. Ayodele Olugbenga E.
- Pastor Adetunji
- Mr. Owolade Oladepo A
- Dr Aremu Ademola
- Dr Olakulehin Olawale

At a Glance

- Founded: October 2006
- Initial Number of Administrative Staff: 2
- Present Number: 5
- Initial Number of Offices: 1
- Present Number of Offices: 2
- Total number of Manuscripts Reviewed till date: 481

Which Departments are the Manuscripts coming from?

Community Medicine	46
Biomedical Sciences	35
Paediatrics	30
Medical Lab Science	28
Surgery	27
Microbiology	25
O&G	25
Nursing	24
Internal Medicine	21
Ophthalmology	20
Family Medicine	18

Psychiatry	15
Haematology	15
Biological Sciences	14
Radiology	14
Anaesthesia	10
Chemical pathology	8
ENT	8
Histopathology	5
Biochemistry	3
Pharmacy	3
Miscellaneous	31

Institutions That has Patronize LTH IRB

LTH/LAUTECH CHS	430
LAUTECH, Ogbomosho	5
Nnamdi Azikiwe University	1
University of Ilorin	2
Osun State University	11
OAU/OAUTHC	13
UI	5
RUN	8
Fountain University	3
Foreign Universities	9

Foreign University	Number
Texila American University	1
MIT	1
Liverpool School of Tropical Medicine	1
Frank Netter School of Health	1
University of East Anglia, UK	1
School of Health & Social Work, England	1
Quinnipac University	1
South Africa	2

Our Clients

Clients	Number
Consultants	238 (53.1%)
Residents	98 (21.9%)
Other Lecturers	70 (15.6%)
Students	48 (10.7%)

Time Frame

Event	Time
Average time before first IRB Sitting on Manuscript	2.6 weeks
Average time to Second IRB Sitting on manuscript	5.8 weeks
Average time taken by Authors to effect corrections:	4.9 weeks
Average time taken by reviewers to complete first review	3.2 weeks
Average time taken by reviewers to complete second review	1.8 weeks
Average Total time from submission to completion	9 weeks
Range	2 weeksto Infinity (LOL)

About LAUTECH IRB

- Serves both the Hospital and the College
- Members of the board had gone for NREC approved trainings.
- Latest training was the EDCTP funded Research Monitoring and Evaluation of Protocols, a 5-day training course in the hospital.
- Started with a one-member secretariat staff in a sparsely furnished office
- Now has:
  - a well-furnished office and a conference room for its monthly meetings.
  - 6-member secretariat staff

LAUTECH IRB procedure

- We have developed Standard Operating Procedures for most of our activities
- The Committee meets once a month to deliberate on submitted articles
- Articles are submitted to at least three peer reviewers, one of which is a member of the committee
- The reviewers are blinded to the identities of authors
- Reviewers' comments are then jointly considered by the committee
- Manuscripts are then sent back to the authors to effect the corrections

Guidelines for submission

- The Researcher should submit
  - 20 copies of abstract of the **study protocol**
  - 4 copies of the full study protocol
  - a covering letter.
- An electronic version on a CD-ROM flash drive should be submitted along with the hard copies.
- Phone numbers and e-mail of the Researcher should also be included during submission of protocol .

Guidelines for submission

- **The protocol should include the following: -**

i. Clear research objectives and rationale for undertaking the investigation in human subjects in the light of existing knowledge.
ii. Subject recruitment procedures.
iii. Inclusion and exclusion criteria for entry of subjects in the study.

Guidelines for submission

iv. Precise description of methodology of the proposed research, including intended dosages of drugs, planned duration of treatment and details of invasive procedures if any.
v. A description of plans to withdraw or withhold standard therapies in the course of research.
vi. The plans for statistical analysis of the study.

Guidelines for submission

vii. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and vernacular languages.
viii. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research.
ix. For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to over dosage should be included.
x. Proposed compensation and reimbursement of incidental expenses.

Guidelines for submission

xi. Storage and maintenance of all data collected during the trial.
xii. Plans for publication of results – positive or negative – while maintaining the privacy and confidentiality of the study participants.
xiii. A statement on probable ethical issues and steps taken to tackle the same.
xiv. All other relevant documents related to the study protocol including regulatory clearances.
xv. Details of Funding agency / Sponsors and fund allocation for the proposed work.

Guidelines for submission

- Undergraduate students are to pay N1, 000.00,
- Residents and others in training are to pay ₦3, 000.00
- Consultants and other categories of workers are to pay ₦ 3,500.00 for the submission.

Account Details

- **BANK:** ECO BANK PLC
- **ACCOUNT NUMBER:** 0024796146
- **ACCOUNT NAME:** LAUTECH-ETHICAL COMMITEE

The Pfizer Trovan case study in Nigeria

- An official inquiry has been set up into allegations that the drug manufacturer Pfizer did not obtain official approval before testing a new drug on children during a meningitis epidemic in Nigeria five years ago.
- The Nigerian doctor who supervised the clinical trial has said that his office backdated an approval letter and this may have been written a year after the study had taken place.

Controversial Ethical Questions

- Who approved the trial?
- Why was Nigeria chosen for the trial?
- How were the subjects recruited?
- Did the parents/guardians sign any informed consent?
- What is the benefit of the trial to the children?
- What measures were put in place to minimize harm?

Ethical Issues

- No ethical approval obtained.
- No informed consent obtained.
- High harm/benefit ratio.
- Victims were not compensated associated injury.

AFTERMATH OF THE TROVAN CLINICAL TRIAL

- Exposed the absence of ERCs in Nigeria.
- Exposed "sharp practices" in local and international researches in Nigeria.
- Raised the need for ethical consciousness in conducting research on human participants.
- Encouraged the formation of HRECs in institutions where research is conducted.

To ask questions, please join the forum at www.oluwadiya.com