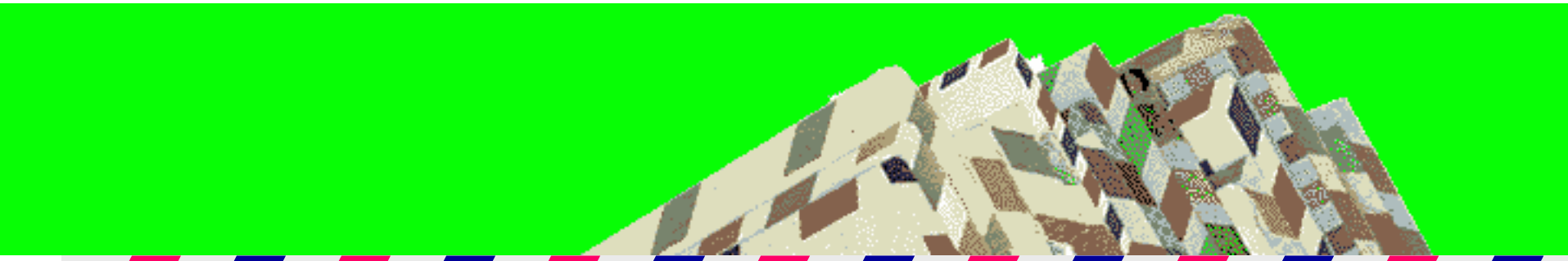
Principles of Surgical Research



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Why do research?

- What are the sources of knowledge
  - Culture and Tradition
    - As varied as human experience!
  - Religion
    - Different religions interpret the world around us differently!
  - Authorities
    - As reliable as their own sources!
  - Science
    - Does science vary according to place and time?

Tools of research

- Motivation
- Strong vision of what you want to achieve
- Proactively work towards that vision
- Take personal responsibility for success or failures
- Disciplined work habits
- Balance between self-development and creative research

How to?

- Where do research ideas come from
  - Observation
  - Prior hypothesis
  - Intuition
  - Knowledge experts
- What should you do about your research ideas
  - Think
  - Read
  - Write

How does science work

- Bacon's scientific method
  - Science is a process of generating generalizable knowledge. It is not an encyclopedic knowledge of the universe
- Popper's Falsification Theory
  - Science begins with a prejudice (theory or hypothesis), progresses by proving that good ideas are wrong so that they can be replaced by better ones

How does science work

- Kuhn's paradigm shift
  - A paradigm is a consensual world view within which scientists work. As time goes on, difficulties arise in this world, becomes intolerable and requires a paradigm shift that changes the old paradigm
- An evolved theory of science
  - All 3 theories help us to gain a deep understanding of science

Science now

- Scientists are Baconians when dealing with their data. They treat it reverence and do not tolerate falsification
- Science is adversarial. Scientists attack each other's theories – to this extent, they are Popperians!
- Science changes perspective leading to new and better ways of understanding the world thereby fulfilling Kuhn's hypothesis of paradigm change!
- Science is always getting better
- Science is peer reviewed

Tools of Surgical Research

- Observational studies
  - Ecological studies
    - Very useful. Here we compare population characteristics to find correlates of disease. For example compare the amount of dietary fat consumed in different countries with the incidence of breast cancer in those countries to see if there is any association. It is limited by unmeasured confounding
  - Case series
    - Popular in surgery because they are easy to perform, require less resources, can be performed at a single center, provides a means for the surgeon to showcase personal skill and methods

Tools of Surgical Research

- Special exposure groups
  - This is useful when the exposure or conditions derived therefrom may be of etiologic significance. For example, if you are interested in the effect of eating meat on a certain disease, then compare people who do not eat meat, e.g. Vegetarians (Buddhists, Adventists), to those who do
- Migrant and secular studies
  - Here we study people of similar origin, some of whom have migrated either voluntarily or forcefully (slave trade) to see whether the occurrence of disease varies across that population across the spectrum of migration. For example, the study of hypertension among blacks in Igbo-Ora, Ibadan, Kingston Jamaica and the USA

Tools of Surgical Research

- Case control
  - In case control studies, we gather people who have the condition of interest and compare them over the same period of time with people who are similar to them but for the fact that they do not have the condition. It is relatively cheap, does not take time but is troubled by problems of recall and selection bias
- Cohort studies
  - Expensive long term study of a group of people for occurrence of condition of interest among them over time. It is the best tool of observational research

Tools of Surgical Research

- Experimental studies
  - Cell culture
    - Here we grow cells *in vitro* and study exposure and the response of the cells
  - Animal experiments
    - We use animal models of diseases or create the condition of interest in the animal and study
  - Controlled trials
    - The characteristics of this method are randomization and blinding. We allocate people by chance to an investigational and a placebo arm and compare their response to exposure of interest

Tools of Surgical Research

- Qualitative methods
  - There is increasing need for the use of these tools in answering questions pertinent to surgical treatment, training and research
  - Includes, ethnographic methods, focus group interviews, key informant interviews, case studies and questionnaire surveys
  - Requires as much care with design, analysis and interpretation as quantitative methods in order to reach valid conclusions

Tools of Surgical Research and Evidence-based Medicine

- These tools have a hierarchy of value, but care must be exercise in applying judgment as this hierarchy is not strict
- Randomized double-blind controlled clinical trials are acknowledged as the most superior basis for evidence-based medicine, followed by the observational studies (cohort>case control>case series>ecological studies), then animal and cell culture studies
- A study is only as good as the design, implementation and analysis
- Some conditions cannot be studied by experimental methods and inference must be drawn from observational studies

Institutions of science

- Where science is done
  - In degree awarding institutions
  - In hospitals
  - Laboratories
- Role of Scientific societies
  - Are like the grand juries of science and conduct of scientists
- Role of journals and conferences
  - Publications and peer review are the currency of science

The rewards of science

- The sheer pleasure of finding things out
- Reward system and authority structure
  - Academic promotion
  - Various prizes and medals by different scientific organizations
  - Endowed chair
  - Election into National Academies
  - Nobel Prize and similar level prizes in different disciplines
  - Immortality

Let us remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who deplore that particular disease be not conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having - Jonas

History of ethical problems in research

- While there was concern about ethical research before it, it was the Nuremberg trial that focussed attention on the need for a code of research ethics
- This was the trial of German Nazi doctors who conducted experiments on prisoners. Prosecutors argued that the experiments violated fundamental ethical standards of civilized society. At that time, there were no codes of ethics for conducting research on human beings and the defense argued that similar experiments were being conducted by the Americans at that time – malaria experiments on prisoners. (*Did the defense know about Tuskegee and if they knew what would they have thought of it*?)

Nuremberg code

- The main components of the code are
  - Requirement for voluntary participation
  - Informed consent
  - Favorable risk/benefit analysis
  - Right to withdraw without penalty
- Largely ignored by medicine, because it was considered legalistic and something created for those “evil” doctors not “us”

1964 World Medical Council Declaration of Helsinki

- This basically builds on the Nuremberg code and adds two additional points
  - That the interests of the subject should always be given a higher priority than those of society
  - That every subject in clinical research should get the best known treatment. This latter requirement has generated intense debate particularly in the context of funded international collaborative research. What is the standard of care that should apply in such studies

Other seminal events

- Beecher's article in NEJM in 1966
- 1973 Congressional hearings on quality of health care and human experimentation
- Main catalyst for this was the Tuskegee Study (1932 – 1972) – a study of the natural history of syphilis in untreated African-Americans who were denied treatment after effective treatment (penicillin) became available and avenues via which they could have treatment were also blocked. Articles from this study were regularly published in the leading medical journals and it took journalistic focus on the ethics of the study to bring it to a halt and worldwide opprobrium

Other seminal events

- but there were others, like
  - 1950 Willowbrook Hepatitis Study – feces was fed to mentally retarded children at an Institution near New York to study feco-oral transmission of Hepatitis A
  - 1960 Jewish Chronic Diseases Hospital Studies – hepatoma cells were injected into the bloodstream of elderly Jewish inmates of an old-peoples home to study implantation of tumor cells
  - 1960 Milgram study of obedience – study of obedience and compliance with instructions which lead to significant psychological morbidity in the participants
  - 1970 San Antonio study of contraceptive pills – some of the women participants who did not wish to be pregnant were placed on placebo

Ethical principles of the Belmont Report and their implications

- These problems led to the codification of additional rules to guide ethical conduct in research. The most influential of these rules is the Belmont Report and its main principles are:
  - Respect for persons
    - Participants must voluntarily consent
    - Informed consent must be obtained
    - Privacy and confidentiality must be guaranteed

Ethical principles of the Belmont Report and their implications

- Beneficence
  - The risks of research are justified by their potential benefits
  - Study is designed to minimize risk
  - Conflicts of interest are adequately managed
- Justice
  - Vulnerable subjects are not targeted for convenience
  - People likely to benefit from research are not systematically excluded

What makes a research ethical

- Is it the informed consent document
  - Not always needed
  - Many of the current problems in research ethics do not have anything to do with informed consent
- Many of the codes used today were derived after crisis and ethical dilemmas so they tend to be reactive

What makes a research ethical

- Current problems in research ethics
  - Use of placebo
  - Phase 1 drug research
  - International research ethics
  - Community engagement and protection of communities
  - Involvement of children
  - Tensions and contradictions exist among the different guidelines
- We need a code that emphasizes the need for a coherent and systematic framework that includes all relevant ethical considerations

Seven requirements proposed by the NIH Clinical Ethics Group

- To serve as a guide for
  - Ethical development
  - Evaluation of clinical studies by investigators, IRB members, funders and others
- To codify the several national and international guidelines which were written in response to crises and therefore tend to focus on preventing new ones

1. Value

- The research must add value. It must be an evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge
- The justification for this is the need for
  - Responsible use of scarce resources
  - Avoidance of exploitation
- Value must be in terms of
  - Scientific knowledge
  - Citizen's understanding of social priorities

Examples of non-valuable research

- Clinical research with non-generalizable results
- Trifling hypothesis
- Substantial or total overlap with proven results
- Results that can never be disseminated
- Implementation of result is impractical, even if effective

2. Scientific validity

- Research must be conducted in a methodologically rigorous manner
  - Clear objective
  - Designed according to accepted principles, methods and reliable practices
  - Have sufficient power
  - Plausible data analysis
- Justification
  - Responsible use of scarce resources
  - Avoidance of exploitation

Examples of Invalid research

- Biased samples, questions, or statistical methods
- Under-powered studies
- Neglect of critical end points
- Could not possibly enroll enough subjects
- Careless, sloppy conduct of research
- Absence of a null hypothesis or clinical equipoise

3. Fair subject selection

- Scientific goals, not vulnerability, privilege, etc. should guide subject selection
- Groups should also not be unnecessarily excluded from the opportunity to participate in research
- Remember that subject selection can affect risks and benefits of a study
- Groups who bear the burden should enjoy the benefits of research endeavors
- Justification
  - Equals should be treated similarly
  - Fair distribution of social cooperative efforts

Unfair subject selection

- Avoid convenient samples when the scientific question does not justify it
- Avoid subjects with compromised ability to protect themselves
- Subjects who qualify but are at substantial risk of being harmed or experiencing more harm should be avoided
- Groups who would be excluded from the benefits of a research should not have to bear the burden

4. Favorable risk-benefit ratio

- 3 conditions need to be fulfilled consistent with the scientific aims of the study and relevant standards of clinical practice
  - Potential risks to individuals are minimized
  - Potential benefits to individuals are enhanced
  - Potential benefits to individuals or society outweigh the risk
- What about research that promises no benefit to participants?

5. Independent review

- Investigators have multiple and often conflicting interests which can distort judgment
- Reassures society
- Must be conducted by peers who have expertise in the field. Can be blinded or open
- There is increasing role for the community, patient advocates and survivors in peer review of research proposals

6. Informed consent

- Purpose
  - Ensure that individuals control their participation in research
  - Ensures that individuals are informed, understand the information and make voluntary un-coerced decision to participate
- Even if people have lost some of their ability to give consent, they still retain the values and sensibilities they had before they lost this ability. This must be taken into consideration in such instance for example in studies that involve unconscious or mentally impaired subjects

7. Respect for enrolled and potential subjects

- Ethics does not stop once the patient signs the consent form (or does not sign the form)
  - Privacy
  - Withdrawal
  - Provision of new information as they become available and where relevant
  - Participants welfare
  - After research information provision

Importance of these requirements

- Universality
- Expertise
  - Clinical investigators must be skilled in research methods, statistical tests, outcome measures, etc. but must also be able to affirm, appreciate and implement ethical requirements
- Ethical boards should consist of people with training in science, statistics, ethics, law and citizens who know social values, priorities, vulnerability and concerns of potential subjects

What is research

- U.S. Federal regulation 45 CFR 46 defines research as “a systematic investigation designed to develop or contribute to generalizable knowledge”
- 2 components
  - Systematic investigation
  - Intent is to develop or contribute to generalizable knowledge

What is not research

- Medical practice, particularly innovative therapy (or non-validated practice) – an activity designed solely for the benefit of the patient but in which the ability of the activity to result in the desired result is to some degree not proven
- Medical practice for the benefit of others, e.g. vaccination, - the goal of the intervention is to benefit a well defined group of people in a predictable way

What is not research

- Public health practice e.g., monitoring of diseases, monitoring of programs
- Quality assessment or improvement
- Outcome analysis
- Resource utilization review
- Investigational or off-label use of products

Science, pseudo-science, non-science and nonsense

- Scientist must have open minds
  - Not so, scientists must hold on but only to proven ideas
- Science must be an open book
  - There is a large component of skill required
- When a new theory comes along, scientist must falsify it
  - Rather scientist try to verify new findings
- Real science is easy to differentiate from pseudoscience
  - Not so

Science, pseudo-science, non-science and nonsense

- Scientific theories are just “theories” that can be proved wrong
  - Characteristics of scientific knowledge are – testability, peer review, known or potential error rate, general acceptance within the scientific community
  - Distinguish between “textbook” science and human knowledge frontiers
- Scientists are always truthful and honest
  - They are humans

More information

- For information about bioethics opportunities and training http://www.westafricanbioethics.net/
- For information about Nigerian code of health research ethics http://www.nhrec.net/