Caribbean Public Health Agency

Preventing disease
Promoting and protecting health
ETHICAL PRINCIPLES IN RESEARCH WITH HUMAN PARTICIPANTS
- “An Overview”

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Overall Objectives:

To ensure all Members and Alternate Members of CARPHA’s Research Ethics Committee, attending CMOs, their Representatives, and Members of their IRBs/Ethics Committees – are familiar with:

- The rationale for ‘research ethics’
- The standards required for the ethical conduct of research
- The standards for the oversight of the research process!
Overview:

• The ‘Ethical Requirements’ for Clinical Research

• The History of Unethical Research with Human Beings

• Ethical Considerations for Research

• The Independent Review of Research

• Ethical Issues During and After the Study

• Summary
Ethical Principles in Human Subjects Research:

• The ethics of human subjects research requires that all research meet the highest ethical and scientific standards.

• All persons involved in conducting research should be fully conversant with the relevant ethical principles of biomedical research and its requirements.
Research Ethics:

• The field of **Research Ethics** is devoted to the systematic analysis of questions addressed by research, to ensure that participants in a study are protected, and that research involving the participants is conducted in a way that serves the needs of participants as well as those of society.
Research Ethics:

Medical practitioners and others who undertake research endeavours should receive prior training in research methodology and research ethics, including the seven ethical requirements for research. Practitioners should be aware that the aims of health care and research are divergent and are sometimes in conflict. Health care aims to benefit the individual patient, and so the doctor has a clear and singular obligation to the patient in the health care setting.
Research Ethics:

Research, on the other hand, aims to increase knowledge that may benefit a wide range of persons or the general society, but does not seek to benefit the particular patient who may be enrolled in the research endeavour. The practitioner who conducts research therefore has various obligations (and incentives) that may sometimes be in conflict.
Research Ethics:

• Many of the ethical issues that arise in research with humans (for example – informed consent, confidentiality, and the doctor’s duty of care) overlap with ethical issues in clinical practice.
“Therapeutic Misconception”

- Patients seeking health care may be invited to be participants in research
- However, it must be made clear by the recruiter – to the potential participant – the difference between health care and research
- “Therapeutic misconception” – occurs when patients think they will be receiving health care only (therapy) - when they are, in fact, being enrolled in research
- Strategies to minimize ‘therapeutic misconception’ include – providing a clear oral and written description of the goals and procedures of research (e.g. Treatment allocation and randomization), and the recruiter having a comprehensive discussion with the potential participant about the voluntary nature of the endeavour and possible alternatives.
Ethical Requirements for Clinical Research:

- **Value** - The research must be valuable

- **Scientific Validity** - The research must be conducted in a rigorous manner

- **Fair Subject Selection**

- **A Favourable Risk-Benefit ratio**

- **Respect for Persons**

- **Informed Consent**

- **Independent Review of Research**

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History of Unethical Research:

• This goes back to 1796 – Edwin Jenner’s Smallpox Vaccine, England:

• This research involved injecting an 8 year-old child with pus from a cowpox infection, and then deliberately exposing the child to smallpox – to establish acquired immunity.

• While this became a great step forward in the fight against smallpox, the exposure to risk to which this child was subjected – would never be condoned by the ‘ethics’ of today!
History of Unethical Research:

• The Neisser case – Prussia, 1898:

• Albert Neisser conducted clinical trials on serum therapy in patients with syphilis. This was done by injecting serum from patients with syphilis into those who were admitted for other reasons, without either informing them about the experiment, or seeking their consent. When subsequently some of these patients developed syphilis, Neisser concluded that the vaccination had failed.

• This was picked up by newspapers, drawing public attention and ultimately leading to the Minister for Medical Affairs issuing a directive requiring that non-therapeutic research must have unambiguous consent!
History of Unethical Research:

• The Little Albert Experiment – United States, 1920:

• This research aimed to demonstrate the phenomenon of ‘human conditioning’, by conditioning an 11 month-old infant to fear rats, by associating them with fear that was induced by circumstances such as a loud noise.

• The research was conducted without the knowledge or consent of little Albert’s parents.
History of Unethical Research:

• The German experiments with unconsenting prisoners in concentration camps during World War II. Experiments included involuntary sterilization, subjection to radiation, freezing – to induce hypothermia, infection of research subjects with malaria and tuberculosis, and other experiments that often lead predictably to extreme pain, mutilation, and death.

• At the Nuremberg trials, 23 physicians were tried for crimes against humanity.
History of Unethical Research:

• The resulting Nuremberg code in 1947 - stipulated that the voluntary and informed consent of the human subject was absolutely essential, and that experiments with humans should only be done when the results would be unprocurable by other methods or means of study.

• This Nuremberg Code became the 1st International Code of Research Ethics!
History of Unethical Research:

• In 1956, a series of experiments were carried out using mentally-impaired children who were deliberately infected with hepatitis A at the Willowbrook State School in New York, USA.
The Willowbrook State School in Staten Island, New York, was an institution devoted to housing and caring for mentally impaired children. The researchers considered Willowbrook to be a good choice for the investigation because viral hepatitis occurred more or less constantly in the institution.

They claimed that “under the chronic circumstances of multiple and repeated exposure… most newly admitted children became infected within the first 6 - 12 months of residence in the institution.”
The Willowbrook Project:

The researchers justified their decision to deliberately infect some incoming children in the following way:

“It was inevitable that susceptible children would become infected in the institution. Hepatitis was especially mild in the 3-10 year age group at Willowbrook. These studies would be carried out in a special unit with optimum isolation facilities to protect the children from other infectious diseases such as shigellosis, and parasitic and respiratory infections which are prevalent in the institution.”

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Consent to participate in the Project:

In the earlier phases of the study, parents were provided with relevant information either by letter or orally, and written consent was secured from them.

In the later phases, a group procedure was used. A psychiatric social worker would discuss the project with the parents during a preliminary interview. Those interested were invited to attend a group session to discuss the project in greater detail.
Consent to participate in the Project:

These sessions were conducted by the staff responsible for in-patient care at the institution, and after the purposes, potential benefits and hazards were discussed, parents were encouraged to ask questions.

Two (2) weeks after briefing, the psychiatric social worker would contact the parents for their decision.
History of Unethical Research (cont’d):

- The Milgram Experiments – United States, 1961-63:

- In these experiments, designed to investigate people’s obedience to authority, the research subjects were deceived about the nature of the research and led to believe that they (in the process of a different experiment) were administering electric shocks to other research participants.

- The aim of the research, which turned out to be very distressing for many of the subjects, was to see how far they would be willing to go in risking harm to other research participants!
History of Unethical Research (cont’d):

• In 1963, three doctors – with the approval of their director of medicine – injected live cancer cells into 22 uninformed, debilitated patients at the Jewish Chronic Disease Hospital in Brooklyn, New York.

• In 1971, a report was made that the San Antonio Contraceptive Study enrolled impoverished Mexican-American women who were seeking contraception. None of the women were told that placebos were included in the clinical trial of the oral contraceptive, and 10 of the 76 subjects (all on the placebo arm of the study) subsequently became pregnant.
History of Unethical Research:

• In the Tuskegee Study (1932-1972), over 400 disadvantaged and misinformed rural black men with syphilis were enrolled to study the untreated course of a disease that was **NOT** confined only to that population in the USA. More importantly, they did not receive penicillin – a safe and effective treatment for syphilis – when it became available in the late 1940s.
History of Unethical Research:

• In June 1987, an article in the Auckland journal exposed an idiosyncratic method of treating carcinoma-in-situ by an Associate Professor at National Women’s Hospital in Auckland, New Zealand. Contrary to established medical opinion at the time, this Obstetrician/Gynaecologist personally believed that this was a harmless disease which rarely, if ever, progressed to invasive cancer.
History of Unethical Research:

• So, for 15 years he simply followed a large cohort of women who were neither told of their disease nor offered any treatment. A number of these women subsequently developed invasive cervical cancer, and several died from the disease.
History of Unethical Research:

- This information was discovered in 2010, by someone researching a book on the Tuskegee Experiments: From 1946-1948, US scientific researchers in Guatemala infected hundreds of mentally ill patients (male and female) with sexually transmitted diseases while they were housed at Guatemala’s National Mental Health Hospital. The scientists injected the patients with gonorrhoea and syphilis – and encouraged many of them to pass it on to others.
History of Unethical Research:

- The experiments were done with the cooperation of the Guatemalan government. The US Public Health Service carried out the experiments under the guise of syphilis inoculations. When it came to light, then US Secretary of State – Hilary Clinton, issued an official apology to Guatemala, and President Barack Obama apologized to President Alvaro Colom, who had called these experiments- “a crime against humanity.”
History of Unethical Research:

• Sports Science muscle biopsy:

• To do research on the oxidation of muscle tissue, a sports scientist wanted to take pea-sized pieces of muscle out of the legs of athletes. The main piece of information on the participant information sheet was that ‘this might hurt a bit.’ No information was given about on-going pain, nor about the possible implications the removal of the muscle might have for athletic performance.
ETHICAL CONSIDERATIONS FOR RESEARCH WITH HUMAN PARTICIPANTS
Ethical Issues Before the Study begins:

- The Study Design
- Ethical Review by an Ethics Committee
- Addressing Conflicts of Interest
Ethical Considerations for Research:

- The Scientific Design of the Research
- The Care of Research Participants
- The Ethical & Scientific Standards and Practice in the Communities in which the research occurs
- The Contribution that the research can make to health
Ethical Considerations for Research:

• The Scientific Design of the Research

This requires a clear scientific objective, a valid and practically feasible methodology, sufficient sample size (power) to test the objective, an acceptable plan for data analysis, and that the research should be able to be implemented.
Ethical Considerations for Research:

• The Care of Research Participants

Where humans must be used in research, researchers should respect their dignity, integrity, and humanity, as well as their fundamental rights and freedoms. Hence, the participant’s health and safety should be monitored throughout the duration of the research, with treatment provided for any untoward event or severe adverse reactions.
Ethical Considerations for Research:

- The Ethical & Scientific Standards and Practice in the Communities in which the research occurs

International Guidelines such as the Declaration of Helsinki, The Belmont Report, and the CIOMS (Council of the International Organization of Medical Sciences) International Ethical Guidelines exist for research with human participants.
Ethical Considerations for Research:

- **The Contribution that the research can make to health:**

Since – to be ethical – research must be **valuable**, many biomedical and health services research seek to improve the health and welfare of individuals and the society in general.

Benefits may include improved health, or medical care and treatment. Research should be responsive to the health needs of a community, and should reflect the priorities of the community in which it is done.
Independent Review of Research
The Ethical Review of Research:

• All research involving human participants should be subjected to ethics review before the commencement of the research.

• Research ethics committees will have the power to require changes in research protocols, and to prevent unacceptable research from proceeding.
Addressing Conflicts of Interest
Conflicts of Interest:

• A conflict of interest may arise when a researcher has a material interest (personal, financial, career, etc.) that may conflict with his/her duty of honesty and integrity.

• Physician-researchers may also have a conflict when they plan to enroll their patients in a study. Here, the desire to serve the patient’s best interests may be at odds with the desire to achieve the objectives of the study.
Addressing Conflicts of Interest:

- Researchers should declare any conflicts of interest to their superiors or to the reviewing body of the research protocol, and should act in a manner that is above reproach.

- Where physicians wish to enroll their patients into a study, to avoid any element of coercion to participate, the objectives of the study and the invitation to the patient to participate should be provided by a third party not directly involved in that patient’s health care.
ETHICAL ISSUES DURING AND AFTER THE STUDY
The Guiding Ethical Principles in Research:

• RESPECT FOR PERSONS

• BENEFICENCE

• NON-MALEFICENCE

• JUSTICE
Guiding Ethical Principles in Research:

• RESPECT FOR PERSONS

*Respect for autonomy* requires that we respect the moral worth of persons by respecting their choices and not acting contrary to persons’ considered judgements, nor withholding information they need to make a considered judgement.
Guiding Ethical Principles in Research:

• RESPECT FOR PERSONS

Respect for persons therefore obligates that informed consent for research be obtained, and that confidentiality of information about research participants be maintained.
Guiding Ethical Principles in Research:

• BENEFICENCE

This ethical principle morally obligates us to act for the benefit of others, and so requires that persons participating in research be treated in an ethical manner by making all efforts to ensure their well-being.
Guiding Ethical Principles in Research:

• BENEFICENCE

From this then follows the requirement that the potential benefits of research be maximized for both the individual participants in research as well as the society, while risks are minimized.

Hence, a **favourable** balance between the potential *benefits* and the potential *harms* of participating in research should exist.
Guiding Ethical Principles in Research:

• NON-MALEFICENCE

This ethical principle requires that, in our endeavours to benefit persons, we should do no harm. Researchers thus have the responsibility to make all efforts to minimize harm in their research activities.

This includes not selecting participants for research who are already burdened or who will not have access to any of the benefits that may accrue from research.
Guiding Ethical Principles in Research:

• **JUSTICE**

This ethical requirement connotes fair, equitable and appropriate treatment and consideration in light of what is due or owed to persons. The *selection of subjects* for participation in research should be fair, and persons should be protected from bearing a disproportionate share of the burdens or risks of research.

The *scientific goals* of the study – and not the easy availability of some subjects – should be the criteria for the selection of research participants. Further, the groups or individuals who bear the risks and burdens of research should be in a position to enjoy its benefits. Also, those who may benefit should share in some of the risks.
Fair Selection of Subjects:

- Unjust social practices and undercurrent racial, sexual, or cultural biases will affect the ethical validity of the research process.

- Participants should not be selected simply because of their easy availability or their reduced autonomy.
Vulnerable Populations:

Vulnerable participants are persons who have a diminished ability to protect their own interests, persons who have a reduced capacity to give informed consent, persons who are not able to understand or communicate, persons who are not in a position to make a voluntary decision, and persons who are at increased risk of harm or increased burden.

Researchers thus have the obligation to be sensitive to the special nature of these individuals.
Vulnerable Populations:

- Prisoners
- Children
- Foetuses
- The ‘mentally disabled’ or ‘decisionally impaired’
- Terminally ill patients
- Persons in dependent positions
- Educationally or economically disadvantaged persons
Vulnerable Populations:

Special justification will be required to invite such persons to participate in research, and the CIOMS Guidelines require that additional safeguards be employed to protect their rights and welfare. This may involve further research regarding their condition, limits to the amount of risk allowed, consent provided by proxy or surrogate decision-making that utilizes the best interests standard, consent ‘monitors’, as well as the on-going monitoring of research.
Assessment of Risks and Benefits:

- Compares predictable risks with foreseeable benefits
- Evaluates the *probability* and the *magnitude* of possible harms
Assessing Risks and Benefits:

- Risks should be identified and minimized using procedures that are consistent with sound research design.

- Researchers should be familiar with the differing nature of possible harms:
  - Physical
  - Psychological
  - Moral
  - Social
  - Legal
  - Financial / economic
Assessing Risks and Benefits:

Examples:

• **Physical** - As in invasive procedures

• **Psychological** - If participants may feel threatened

• **Moral** - If possible harm to a person’s interests, integrity, etc.

• **Social** - If a person’s HIV-positive status may be inadvertently revealed

• **Legal** - If information about illegal substance abusers are revealed to the police

• **Financial / economic** - If disclosed information about HIV-positive persons may result in loss of jobs, etc.
Assessing Risks and Benefits:

• Potential benefits from the research should be identified and maximized.

• Risks and benefits to individual participants should be compared. The more likely or more severe the potential risks, the greater should be the likelihood and magnitude of the prospective benefits.
Informed Consent:

- A basic moral principle:
  - Imposes the duty for others to respect the worth of each individual
  - Recognizes that persons exercise their right to the fullest when in possession of all important information
An Ethical Requirement:

- The principle of informed consent requires that health professionals, before any diagnostic or therapeutic procedure is carried out, explain to the patient what is involved in order to secure the understanding and consent of the patient to proceed.
The Purpose of Informed Consent:

• To enable self-determining choice

• To protect patients from harm

• To encourage medical personnel and researchers to act responsibly in interactions with patients and research participants
Conditions necessary for Informed Consent:

- Pre-conditions

- Informational Elements

- Consent Elements
Confidentiality & Privacy concerns:

• Confidentiality in research must not be breached without the participant’s consent, and it imposes the duty of effectively securing any access to personally identifying information.

• Health care research based on a retrospective review of patient records carries the risk of a breach of confidentiality. This may occur at the identification of, and access to the person’s chart. However, individual identifiability should be blocked at subsequent stages.
Confidentiality & Privacy concerns:

- In Epidemiological studies, if identifiable data is to be used and prior consent is not being sought, the investigators should show in their protocol why it is ethical for the requirement of consent to be waived, and that adequate means exist to ensure the confidentiality of the data.

- When confidentiality issues are unclear, the advice of a research ethics committee should be sought.
On-going Monitoring of Research:

• Where considered necessary – e.g. in research involving more than minimal risk, ethics committees should monitor on-going research.

• Data for all research should be properly recorded and securely stored.

• The principal investigator has the obligation to provide monitoring information to the research ethics committee, including the reporting of any adverse events.
On-going Monitoring - Respect for Persons:

This includes respect for the enrolled participants - such as ascertaining:

- ‘Will their privacy be protected?’
- Do they have opportunity to withdraw from the research?
- Will they be provided any new information of importance during the study, and a summary of ‘results’ at the end of the study?
- Is their well-being being monitored?

- Adequate provisions for treatment of adverse conditions?
SUMMARY…
What makes Clinical Research Ethical?

The 7 Ethical Requirements:
- Value
- Scientific validity
- Fair Subject Selection
- Favourable Risk / Benefit ratio
- Respect for persons
- Informed Consent
- Independent Review of Research

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Responsibilities of the Researcher:

• S/he should select research participants fairly, and safeguard their well-being

• S/he should be sensitive to the special nature of vulnerable subjects

• S/he has the duty to secure all personally identifying information on research participants

• S/he should seek consent only after all the elements of the informed consent process have been satisfied
CARPHA Thanks You!

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