Introduction to Research Ethics

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How important do you feel ethics are in clinical research?

- Very important at all aspects
- Important as related to human subjects only
- Important as related to IRB only
- Important only to address research as ethical
Many ethical concerns must be addressed when research involves human participants. People will accept risks and inconvenience with research that leads to advanced scientific knowledge or when it benefits others.

However it is important to conduct such research according to strict ethical standards in order to gain the trust of the public so that people are willing to participate in clinical research.

1. Institute of Medicine, 2003.
Ethical Principles

Three ethical principles guide research with human participants.

The Principle of:

1. **Respect for persons** – requires investigators to obtain informed consent from subjects, to protect vulnerable or impaired subjects, and to maintain confidentiality.

2. **Beneficence** – requires that the research design be scientifically valid and the risks or burden of the research be acceptable and not outweigh the likely benefits.

3. **Justice** – requires that the benefits and burdens be distributed fairly, especially among those of vulnerable populations. Vulnerable populations include the cognitive or communicative impaired, institutionalized, social and economical disadvantaged, children, pregnant women, elderly, and terminally ill.

Federal Regulations for Research on Human Subjects

- Federal regulations are proposed to guarantee that human research is conducted in an ethical manner.

- These regulations strictly apply to all federally funded research and to research submitted to the US Food and Drug Administration (FDA) for new drug or device approval.

- Most universities and other research institutes also require all human research to adhere to the federal guidelines.

Protection for Human Subjects

The federal regulations enforce two protective methods for human subjects:

1. Institutional Review Board (IRB) approval
2. Informed consent
Nuremberg: The Doctors’ Trial
(December, 1946–July, 1947)

- Human experimentation (unconsenting prisoners)
  - endurance at high altitudes and temperature extremes
  - inoculation with pathogens
  - mutilating experiments on bones, muscles, nerves

- 23 Defendant Nazi doctors
  - war crimes
  - crimes against humanity
Doctors’ Trial Verdict

- 23 doctors on trial
  - 15 were found guilty
    - 7 were hanged in June, 1948 (4 physicians)
    - 5 received life sentences
    - 3 received 10–20 years
  - 1 acquitted, guilty of SS membership
- 31 lesser staff tried and convicted
  - 22 sentenced to hang
- None of the doctors admitted wrong-doing
The Nuremberg Code
(based largely on Alexander’s and Ivy’s testimony)

“1. The voluntary consent of the human subject is absolutely essential. This means the person involved should have 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, and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.”

- full disclosure
- competent consent with understanding
- voluntary

All the elements of informed consent
Case One

- A study was implemented in Northern Asia to study the effects of a herb on cancer prevention. In this country, there is no IRB and basically important to complete the study in an ethical manner as determined by the investigators.

- The investigators found an important association of the herb and cancer prevention and submit there findings for publication.
As a member of the journal’s editorial board, you

- **A** reject the paper outright as there was no IRB review

- **B** accept the paper as good science

- **C** Accept the paper but have the authors include a statement that this work did not have IRB approval

- **D** Accept the paper but write an accompanying editorial that the study was basically completed in an unethical manner
Research Misconduct

Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

- **Fabrication** is making up data or results and recording or reporting them.
- **Falsification** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
- **Plagiarism** is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.
- **Research misconduct** does not include differences of opinion.
Reasons for Research Misconduct

- Career pressure
- Laziness
- Ease
- Fairly safe – low chance of getting caught
Plagiarism

- Any attempt to represent the work of another as his/her own work.
- This includes substantially restating the work of another person or persons in any oral or written work without citing the appropriate source, or
- collaborating with someone else in an academic endeavor without acknowledging that person’s contribution.
Self Plagiarism

- Multiple publication of the same content with different titles.
- Includes publication in different languages
Ghost Writing

- Phenomenon where someone other than the names authors contributes to the writing.
- Typically done with industry support
Any individual that suspects an offense of academic misconduct has occurred, shall report this suspected breach to the appropriate departmental chair or to the dean.

When a case comes to a department chair, s/he should then notify the dean of the graduate school. The dean shall conduct a preliminary investigation to determine that sufficient evidence exists for the case to go forward.

In cases that require a hearing, the dean shall notify the honor council.
Rationale for Academic Discipline

- No honest student shall be put at a disadvantage because of the dishonesty
- Penalties should be compatible with the misconduct
Academic Misconduct

- Defined as a student’s conduct which intentionally misrepresents his/her academic accomplishments, or which jeopardizes the fair judging of another student’s academic work
Case TWO

- A second semester 1st year international student with English not as a first language is taking an advanced subject class.

- The assignment is the completion of an essay addressing a class related issue.

- The writing is superb and you are suspicious and do a Google search and identify several paragraphs that have been copied from a webpage without citation.
As the instructor, do you

- A] Tell the student to be careful and send the student to English class
- B] Turn the student to honor council
- C] Assign the student an F for the actions
- D] Explain what is wrong and have the student repeat the exercise
Case Three

- A second semester 1st year student is ill during the mid-term exam and requests to take the exam at a later date – this is approved by the instructor.

- After recovery, the student is having lunch with a classmate and the exam is discussed. The classmate discusses the content of the exam such that the student can focus the study and preparation.

- The student scores the highest grade on the exam with a score of 97. The next score was a 71 with all other grades below 65.

- Other students report to you – the instructor – that collaboration was suspected.
As the instructor, you

A] Turn the student and the fellow student to honor council

B] Do nothing, there was no real cheating

C] Give the student a 0 for discussing the test

D] Throw the student’s test out and let the final count twice
Ethics and Study Design
Forms of scientific data misconduct include:

- **Obfuscation** – the omission of critical data or results. Example: Only reporting positive outcomes and not adverse outcomes.

- **Fabrication** – the actual making up of research data and (the intent of) publishing them.

- **Falsification** – manipulation of research data and processes in order to reflect or prevent a certain result.

- **Bare Assertions** – Making entirely unsubstantiated claims.
Risk is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study. Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.

Minimal risk exists where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Risk above this standard is more than minimal (moderate, maximal) and that imposes limitations on the conduct of the research and increases the requirements for monitoring. It also requires more stringent approval processes when studying children or otherwise vulnerable populations. Increased risk should be accompanied by the probability of appropriately increased benefits.
Blinding refers to a process whereby the participant does not know whether he/she is receiving an active agent or a similar appearing inactive substance or mock procedure.

Double blinding is a process whereby neither the investigator nor the participant knows which agent the participant is receiving. Usually the research pharmacy holds the master list in case there are complications. Over the course of the last 30 years it became apparent that blinding both participants and research teams reduced biases in the results of studies where subjective elements were important. One result that is almost invariably subjective is the adverse event profile. In the absence of blinding very serious biases have occurred.
Blinding

- Sometimes the effects of the agent in question are so obvious that true blinding is impossible.

- For example, if a weight loss drug were immediately effective, then the results would be obvious to everyone. Under those circumstances special attention has to be given to unbiased evaluation of adverse events, and conflicts of interest must be avoided.
Equipoise

The concept behind equipoise is that in order for a therapeutic trial to be ethical there has to be genuine uncertainty as to the relative efficacy or safety of the treatment arms. Is this new drug better than placebo? Is drug A more efficacious or safer than drug B? In theory, if we knew the answer, there would be no reason to do the trial. In order for a clinical trial to be ethical, then either:

- The individual investigator has genuine uncertainty regarding the comparative therapeutic merits of each arm, or

- The medical community has genuine uncertainty regarding the comparative therapeutic merits of each arm.
Arguments have been made that true equipoise rarely exists because previous research, whether it be in cells or animals or in small groups of humans, usually suggests that the proposed treatment has a better than 50% chance of being effective.

In fact, those sponsoring clinical trials have to invest so much money and effort that they would hardly take the risk of such an undertaking unless they felt that the evidence supporting the efficacy of the intervention was reasonably strong. The FDA would not permit a Phase 3 trial unless the preliminary evidence was promising.
Case Four

- An investigator has implemented a double-blind study of an herb concentrate vs. placebo and the increased libido. The study is well designed and powered. The measure of libido is a self-report.
- About mid-way through the study, it is observed that about 25% of the participants report a discoloration of urine.
- After review of biochemistry – it seems reasonable that the herb is causing the discoloration.
- At the conclusion of the study, the herb has been found to significantly increase the libido of many women and plans are to market the product accordingly.
As a co-investigator on the project, you

- A] declare the study results as invalid as blinding may have been violated
- B] present the results as planned – there is no evidence that the suspected un-blinding affected the results
- C] Modify the analyses plan removing those women who reported the discoloration from the analyses
- D] Proceed with the marketing. This is an herb not a drug and there is no potential harm
Conflict of Interest
Conflict of Interest:

a. Are these analyses to involve a for-profit corporation?

b. Do you or any member of your Writing Group intend to patent any process, aspect or outcome of these analyses?
CONFLICT OF INTEREST
Authors of research articles should disclose at the time of revision any financial arrangement they may have with a company whose product is pertinent to the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial decision, but if the article is accepted for publication, a disclosure statement will appear with the article. Because the essence of reviews and editorials is selection and interpretation of the literature, the Journal expects that authors of such articles will not have any significant financial interest in a company (or its competitor) that makes a product discussed in the article.
Case Five

- A reviewer is reviewing a manuscript regarding the use of a hypertension agent and some dramatic results.
- The results clearly support the use of the agent and indicate better blood pressure control compared to another agent.
- The reviewer is on the speaker bureau for the company with the comparison agent, and is aware of significant confounders that were not considered in the current paper as this information was part of unpublished results associated with the second agent.
- Revealing these issues would lead to a revised manuscript with less dramatic findings in the comparison.
As an advisor to the reviewer

- **A]** Indicate the conflict and do not do the review.
- **B]** Indicate the conflict – and determine if editor would still like this review.
- **C]** There is no conflict as the reviewer has no relationship with the authors or sponsoring company – do the review indicating no conflict.
- **D]** Review the paper, accept the paper, and provide a commentary.
Ethical standards violation

- Standards of human subject protection is violated.
The use of human subjects in research at MUSC falls under the jurisdiction of federal regulations (45 CFR 46 and 21 CFR 50 and 56). MUSC investigators are granted the privilege of using human subjects under normal assurance to the government that research conducted at MUSC complies with these regulations protecting human subjects.
Review by IRB

- The research is sponsored by this institution, or
- The research is conducted by or under the direction of an individual in connection with his/her institutional responsibilities, or
- The research is conducted by or under the direction of an individual who is receiving remuneration from the institution, or
- The research is conducted by or under the direction of an individual using any property or facility of this institution, or
- The research involves the use of this institution's non-public information to identify or contact human research subjects for prospective subjects, or
- The institution's name is used in any way in connection with the study including procurement of sponsorship, announcement or advertisement or other recruitment of subjects.
It is the responsibility of the IRB to safeguard the rights and welfare of human subjects. To this end the Board is obligated and authorized to:

- Ensure that subjects are adequately informed of the nature of the study;
- Ensure that subjects' participation is voluntary;
- Ensure that the benefits of a study outweigh its risks;
- Ensure that the risks and benefits of the study are evenly distributed among the possible subject population; and,
- Suspend human subjects activity that violates regulations, policies, procedures, or an approved protocol, and report such violation and suspension to the Institutional Official.
Required Training

- The Institutional Official, IRB Chairs and Human Protections Administrator are required to successfully complete the OHRP Assurance Training Module.

- Principal Investigators, Co-investigators, or investigators identified on any human subjects research protocol (which includes faculty, collaborators, consultants, post-docs, house staff, fellows, technicians or others who will play a substantial role in the human subjects research, including a major authorship role when work is reported) individuals responsible for obtaining informed consent research study coordinators and full-time research nurses.

- first year graduate students
Case Six

A third year clinical investigator has developed a proposal to assess de-identified existing data from electronic medical records. As exploratory analyses, she determines her hypothesis is supported with a simple assessment. With high enthusiasm she developed an abstract for a meeting she did not originally intend to submit. Her abstract is accepted for oral presentation and published in a major journal. A colleague attends the conference and is angry as he was unable to submit his work due to IRB approval time limits. He turns her over to IRB.
As a member of IRB advisory committee, you

- **A**] Reprimand the PI, but this would have been exempt.

- **B**] Tell the colleague to get over it, this is a minor issue not worth a full investigation.

- **C**] Recognize the violation as serious and have the incident documented as such in her University promotion file.

- **D**] Mandate her to retake the ethical research course
Authorship on Manuscripts

Ethics class
An “author” is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications.

In the past, readers were rarely provided with information about contributions to studies from those listed as authors and in acknowledgments.

Some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research.

Editors are strongly encouraged to develop and implement a contributorship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.
Authorship Rank Determination

- Establishment of a process to establish and criteria for process BEFORE any writing
- Implementation of the process for each manuscript
Case Seven

- A student completes the three papers required for dissertation.
- Two of the papers are submitted, revised and accepted.
- The third is submitted with revisions requested.
- The graduate accepts a new position at different institution and begins a new area of research and finds the revisions for 3rd paper too time consuming.
- The mentor decides to complete the revisions and re-submit changes the corresponding and lead author accordingly. Justification – the lead author accepts the responsibility of the content.
As the student/graduate

- **A**] Accept with appreciation – another paper
- **B**] Write the dean and chair about the unprofessional behavior of the mentor
- **C**] accept but indicate to the mentor you will never publish again
- **D**] write a letter to the editor “clarifying a few points” and indicating who the real leader of the study was.
Case Eight

- A team of clinical and analytical investigators submits a manuscript from a clinical trial to a major clinical journal.

- The paper involves a major statistical comparison and finding.

- The author team recognizes the contribution of the senior analyst as last author on a list of 12 authors.

- The analytical investigator feels shorted indicating that the first 3 authors are typically noted and there is no true senior author.
You are a member of the writing team identified to resolve the issue

- **A**] Just move the analyst to 3rd author
- **B**] Make the analyst the corresponding author
- **C**] Explain the significance of the senior author slot
- **D**] Gather all author together with a poll for the author tank of the analyst
Fellowship in Clinical Research Ethics Certificate Program
CERTIFICATE OF COMPETENCE IN CRE

http://www.values.musc.edu/
Fellowship in Clinical Research Ethics

Certificate Program

The Institute of Human Values in Health Care
and the
South Carolina Clinical and Translational Research Institute
hereby certify that

Recipient’s Name

has successfully completed this competency-based Program and is therefore awarded
The Certificate of Fellowship in Clinical Research Ethics.

Awarded at Charleston, South Carolina, on the eighteenth day of May, 2012.

Vice President for Academic Affairs and Provost
Principal Investigator
South Carolina Clinical and Translational Research Institute
Director
Institute of Human Values in Health Care
Value

• Surpasses CITI certification in substance, value
• Counts toward promotion and tenure
• Courses taught by professionals from broad range of disciplines
• Enhances knowledge base, competencies of CIs
  – evidence of relevant competency ➔ grant apps
  – likely to ➔ a better score
• Improves competitiveness of grant applications (especially NIH)
Innovation, Uniqueness

• Unique structured education and training program
• Addresses competencies required of Cls
  – 8 certificates awarded 2012
  – 25 certificates awarded 2013
• Publish program in peer-review journal
  – Submitted to Academic Medicine
The Fellowship in Clinical and Translational Research Ethics Program

• Created as part of the Clinical Research Ethics Core of the South Carolina Clinical and Translational Research Institute.

• Designed to provide health professionals who are interested in clinical research ethics with sufficient background in that discipline to warrant special recognition in the form of a Certificate in Clinical Research Ethics.
The Fellowship in Clinical and Translational Research Ethics Program

- Comprises several components: a one semester, one-credit course in research ethics, Ethical Issues in Clinical Research and Advanced Ethical Issues in Clinical Research
- Clinical Research Ethics Seminar Series
- Selectives
- All courses are available online.
- The fellowship can be completed in one year or two.
Clinical and Translational Research Ethics Core Competencies

• Protection of Human Subjects
• Study Design and Analysis
• Research in Communities
• Dissemination of Research Results
• Conflicts of Interest and Misconduct in Research
Protection of Human Subjects

• Understand the fundamental principles of the protection of human subjects, the main authoritative bodies, relevant codes, and scope of enforcement;

• Determine risk-benefit ratio of research protocols, balancing risks against potential outcomes, and critique protocols for risks to human subjects;
Protection of Human Subjects

- Describe the elements of informed consent, including ensuring voluntariness and decision-making capacity of participants, avoiding undue influence or coercion, and providing details of the risk-benefit calculation;
- Apply the main regulatory precepts, rules, guidelines, codes, and professional standards in the conduct of clinical and translational research;
- Ensure fairness in recruiting participants and in distributing the benefits and burdens of research;
Protection of Human Subjects

• Understand and critique special issues that arise in research with vulnerable participants and the need for additional safeguards;

• Adhere to all institutional review board (IRB) procedures and describe the principles of research documentation, validation, and audit;

• Ensure appropriate levels of privacy protection throughout all phases of a study;
Study Design and Analysis

- Describe the basic principles and practical importance of proper study design and analytical techniques;
- Discuss the importance of data and safety monitoring plans and boards;
- Use bioinformatics ethically in clinical and translational research;
Research in Communities

• Recognize the demographic, geographic, and ethnographic features within communities and populations when designing and critiquing clinical studies

• Summarize the principles and practices of community-engaged research, including its ethical complexities and cultural sensitivities.

• Describe cultural and social variation in standards of research integrity;
Dissemination of Research Results

• Determine authorship using relevant standards and criteria;
• Describe the role of peer review in funding and publication;
• Avoid irresponsible practices, such as duplicate publication, redundant publication, and copyright violation;
Conflicts of Interest and Misconduct in Research

• Identify and manage conflicts of interest in research, including conflicts in financial affairs, intellectual property, employment, and industry collaboration.

• Identify and manage conflicts of interests associated with research industry collaborations.

• Identify, investigate, and report misconduct in research — fabrication and falsification of data, and plagiarism.
Application for Fellowship in Clinical Research Ethics Certificate Program

Personal Information:

Name
Address
Telephone
E-mail
Date of Birth
Gender
Education:

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Personal Statement:

Why do you want to enroll in this Fellowship? How do you expect to use the knowledge you gain? How do you anticipate you will use the Certificate?

::Please attach response (No more than 250 words, please)

Send completed form to Megan Fier, 25 Courtenay Drive, MSC 295, Charleston, SC 29425 or to fier@musc.edu (843-876-4843)
http://academicdepartments.musc.edu/humanvalues/

Queries to Dr. Robert Sade,
sader@musc.edu (843-876-0182)