2012 SAEM Ethics Curriculum
Module 12: Research Ethics

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ACGME EM Milestones:

- *PROF1: (Professional values)*
- *PROF2: (Accountability)*
- *SBP2: (Systems-based management; cost effective care)*
- *SBP3: (Technology: use effectively and ethically)*

Review 5.12.12

I. Research Design
II. Ethics of Authorship
III. Vulnerable Populations
IV. Subjects' Rights and Informed Consent
V. Research funding and conflicts of interest

12.1. Research Design

Objectives:

1. To describe the ethical responsibilities of principle investigators and their role in research design.

2. To describe considerations for when waiver of consent might be considered in study design. (Note that this is in contrast to exemption from consent, which is described in a later section.)

12.1.1 Case Study - Prehospital Study design:

A principle investigator is researching the use of prehospital resuscitation for patients who are found to be in suspected cardiac arrest on arrival by EMS. The investigation involves a novel approach to resuscitation that currently has not been shown to be either beneficial or detrimental for your study population.

12.1.1 Questions

1. How will some fundamental principles in ethical research guide your study design?

2. How should study design be outlined in order to protect the rights of the study population?
3. How is "Exception from Informed Consent" defined? How does it apply in this example?
4. If patients are enrolled using EFIC what, if any, obligations are there to the study population after enrollment?

Background Information:

Our ethical responsibilities as physician scientist are cemented in our duties as physicians. The patient's autonomy, distribution of benefit to all patients, and above all "do no harm" are the values that ensure patients are treated ethically. As autonomy, justice, and beneficence are principles to be maintained by all physicians, further protection must be done for patients who are potential subjects of research.

Emergency Medicine is in a unique position when compared to other specialties as many patients presenting to the emergency department do not have decision-making capacity (see more in section IX-D Informed Consent in the Emergency Department). It is therefore of the utmost importance that research design is optimized to protect patients and glean as much data as safely, ethically possible. The study design must ascertain what is to be gained from the study, and whether the study population is at undue risk, especially if other alternatives are available. Especially in studies that involve patient centered outcomes, predefined safety measures, such as time points when outcomes can be assessed for positive or negative effects, need to be in place to ensure patients are protected from adverse outcomes. Prospective measures defined prior to the start of the study will aid in the ability to assess for a greater the question at hand. Finally, the addition of blinding of the investigator, the patient or both will provide further support for the outcome measures from the data set.

In the example above, the targeted patient population is unable to give informed consent, and is in extremis, which can qualify the study for "exception from informed consent" (EFIC). As defined from the FDA, EFIC can be utilized if the following four conditions are met:

1. the patient is in a life-threatening situation necessitating the product's use,
2. informed consent cannot be obtained,
3. there is not enough time to wait for a legal representative, and
4. there is no approved equal or better alternative therapy.

This unique application to the informed consent process has been utilized in emergency medicine for pre-hospital medicine and stroke trials. The notion of emergency exception from informed consent has not been shown to be disseminated throughout the general population. Additionally, thoughts from communities about such practices vary and currently haven't been delineated. The researcher must ask for the each study design:

would the study be available for deferred consent in which study patients/authorized representatives are consented? Recent research in Europe has shown the general population has greater acceptance when patients enrolled in studies using EFIC, the patient or their representatives are told of the study after they have already been enrolled.

One would need to assure in the above example that the intervention is randomized, blinded, with predefined enrollment check points to ensure the treatment is not grossly advantageous/ disadvantageous, with calculated power to accurately predict outcome. The ethical questions of enrolling the patient when they cannot consent under EFIC would apply, as would the understanding that the question could only be answered by the method described and not using an alternative subject population, and does not go against another better-proven method.

Research design has over the last century been developed and has evolved to ensure the data presented are valid and accurate. The next step in our evolution of research design is to maintain accuracy and validity while incorporating ever higher ethical standards to maintain the highest regard for our work.

12.2. Ethics of Authorship

Objectives:

1. Define authorship.
2. Define what substantiates a significant contribution to a work such that a person is listed in the byline.
3. Discuss the implications of granting inappropriate credit to a person on a manuscript.

12.2.1 Case Study – authorship issues between student, resident, faculty:

An emergency medicine resident has just finished her research project. She has written a paper with the guidance of a faculty advisor, and the project is meant to be submitted to a peer-reviewed journal. Prior to submitting for publication, a premedical student who helped with the enrollment of subjects by obtaining informed consent and who also collected data asks if you are going to place his name as an author. The student enrolled ~20% of the patients, and entered data from the medical record, but did not do analysis, and did not help write the work. Do you include him as an author?

12.2.1 Study Questions

1. Should the student be included in the byline in this case?
2. What and how should an author contribute to be included as a credited author?
3. Should journal editors limit the number of authors on a manuscript?
4. By what other means could the student be recognized?

Background Information:

Peer review is considered the standard practice for medical journals. Through an extensive vetting process, only a fraction of the works submitted is published each year. As such, only the most relevant work is selected, which serves to further medical science. It goes without saying then that the authors who are named on the research are responsible for their work and the implications to medical science. Authorship recognition has changed over the years from simple honorary naming of chairmen to each author signing disclosure forms stating their contribution to the submitted manuscript.

Our professional guidelines now state that, in order for authorship, each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One author should take global responsibility for the integrity of the work, from initial concept to finished work. The International Committee of Medical Journal Editors (ICMJE), have defined authorship credit as "(1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published". In order for authorship to occur conditions 1, 2, and 3 must all be met.

In our example above while the premedical student was instrumental in the acquisition of data, he did not help write the article, nor was final approval sought prior to submission. As such there is substantial reason not to include him as an author. As current research is less often done solely by the primary investigators but by dedicated research personnel, the role of research assistants in authorship becomes more confusing. If someone enrolls 100% of patients into the study, no matter how well thought out and designed of a study, it could not have been completed without their assistance. The weight should be placed on the principal investigator to assess according tot eh ICMJE and thus determine if the qualifications of authorship are met. It is our duty as physician researchers to uphold these standards and to the best of our abilities challenge us to abide by them.

12.3 Vulnerable Populations

Objectives

1. Define a vulnerable population in research.
2. Describe the ways to protect vulnerable populations in research study design.
3. Describe situational vulnerability and how this might relate to patients in the emergency setting.

12.3.1 Case Study – recruitment and monetary incentives:

You are the principle investigator of an ED study that seeks to determine the efficacy of use of a new drug for cocaine related acute coronary syndromes. A patient presents with chest pain after cocaine use. He is alert, clinically stable, pain free and without ECG changes or initial cardiac marker elevation. He is thought to be able to give informed consent and meets the entrance criteria of the study. He is indigent and each participant enrolled will be given free cardiac clinic follow-up visits that will include transportation and costs and an incentive of $150 upon completion of 2 follow-up visits. The emergency medicine residents working in the ED are asked to recruit "any patient they take care of with cocaine chest pain".

12.3.1 Study Questions

1. Beyond the traditional vulnerable populations defined by research oversight committees -- such as children, prisoners and the mentally ill -- in the case above what types of vulnerabilities might exist?
2. How could the study design account for subject vulnerabilities?
3.

Background Information:

Physicians who engage in research are more often than not in positions of power over their patients and hold influence over them. The responsibility of the physician is to recognize this power advantage and to protect the patient in emergency research. Certain populations are more at risk than others; traditionally these have included children, prisoners, adults with limited decision making capacity and non-English speaking patients. In the past, these patient populations were labeled "vulnerable" and these populations were not included equally in research for fear of exploiting their vulnerability. Researchers have recognized that these populations need to be included, in research studies because exclusion withholds the very real potential benefit for these persons and keeps them at an unfair disadvantage. The National Bioethics Advisory Commission (NBAC) has stated that a subject's circumstances, which are situational,

create diminished autonomy and therefore make them vulnerable. Thus, exclusion of vulnerable participants may constitute unethical research if those persons who are vulnerable are most likely to benefit from the research. The NBAC recommends that investigators not exclude persons from research, but importantly, "change the design so that it does not create situations in which people are unnecessarily harmed".

Despite a heightened presence of local and federal oversight, abuses of human research participants still occur. Especially susceptible are vulnerable persons. The responsibility for ethical research protocols first lies in the hands of the investigator. The MBAC model has encouraged shifting enrollment criteria from classification to situation. Vulnerable persons who are at risk from enrollment in research are separated into two categories: either having difficulty giving/obtaining/understanding informed consent due to impaired decision making capacity, and those at risk of exploitation. Decision making capacity is covered in a later section but of focus here is the patient population who are at risk of exploitation. Six core caution areas have been identified where investigators should examine the need for special protections:

1. Persons who are unable to sufficiently comprehend information, deliberate and make decisions about participation in research. This represents the patients who have low literacy levels, patients with English as a second language, and unrecognized cognitive impairments.
2. Participants who answer to other formal authorities who may have independent interests. This is easily recognizable as prisoners and patients who are inpatient/involuntarily committed to psychiatric facilities.
3. Employees and students where an informal authority difference exists, where the employee/student may feel obligated by the researcher to participate.
4. Patients where no other satisfactory standards exist,
5. Patients who belong to an undervalued group
6. Patients for whom there is a disadvantage to goods and services.

In our example above, the patient belongs both to a undervalued group and disadvantages are present. The prospective enrollee is both homeless and addicted to drugs and the compensation and treatment puts him at undue risk. It is not to say this population does not need to be included but safeguards need to be in place to ensure their safety. If the patients enrolled are all offered the same benefits, there is not enrollment prejudice based on vulnerability, and the patient could be enrolled. What would be better in this example is for the physicians to screen instead of enroll the patient and have a dedicated research coordinator who enrolls patients to ensure equality and protect the vulnerabilities of the different patient population. The duty is not to exclude this patient from the benefits of research but to ensure adequate protection from undue bias.

12.4. Subjects' Rights and Informed Consent for EM Research

Objectives

1. Define the moral principles for research on human subjects.
2. Defines the ability of a person to give informed consent.
3. Describe other methods of enrollment besides Informed Consent.
4. Describe the unique moral challenges relating to research in an emergency setting.

12.4.1 Case Study

A new computer program is being investigated as an adjunct to physicians' decision on disposition of patients with chest pain. All patients with chest pain are considered eligible for enrollment. The study represents only minimal risk to the patients, as the researcher only needs to screen for chest pain and ask the physician a few clinical questions not involving patient identifying information. Do the patients need to give informed consent in order to be enrolled?

12.4.1 Study Questions

1. What are the guiding principles of to obtain informed consent?
2. What are the general requirements for capacity?
3. How can a research study qualify for waiver of informed consent?
4. What are some alternative methods of informed consent? Are they unto themselves or can they be combined?

Background Information:

Our past transgressions have guided and developed into the ethical principles that govern research today. Specifically, research that involves human subjects must include respect for people as autonomous agents, beneficence in maximizing the benefits and minimizing the burdens for research subjects, and justice in equitably distributing the benefits and burdens of research. This was born, initially from the Nuremburg Code, subsequent Belmont in 1979 and ultimately the Common Rule, adopted in 1991. All have focused on the consent process of enrolled patients, keeping their rights at the forefront.

In order to achieve informed consent, decision-making capacity (DMC) must be established if informed consent is sought. DMC is not the same as competence (a legal and global determination). DMC consists of four components: Understanding,

Appreciation, Reasoning, and Choice. A challenge in emergency medicine research is to be able to explain in such a manner that patients can understand what is being asked of them. The Office for Human Research Protection only guides us in writing to state, "documentation must be written in "lay language"". While this is ambiguous, it has been shown most informed consent documents are written at the level of a 6-8th grade level. Striving to write at a language level of the lay population, consent documents still often contain medical language that most lay people do not understand.

The case study above uses a non-invasive example, but our research in emergency medicine is not always as risk-free. Stroke related research involving thrombolytics and the informed consent process has been particularly problematic, since the ability to understand the risks and benefits of a study in someone whose autonomy is impaired or lost, even with surrogates comes into question. Exception from Emergency Consent (or EFIC) mentioned earlier in this section has allowed research to progress in certain instances. The perception by the population in the United States, though, is unclear. While a majority of lay people support the research ideas and what they are trying to accomplish, only a slight majority (55%) would want to participate. In Europe, trials that have met EFIC standards for enrollment have been perceived positively by the population. Such research incurs less objection when participants are given information regarding IRB approval and details of the study after enrollment has been completed. This could be a mutual ground for the future of the United States, where patients are enrolled using EFIC and then afterwards the patient or their representative is informed of the research study and it's implications.

In the current example, exception from informed consent can be applied since it meets the following standards: research involving no more than minimal risk, the rights and welfare of the subjects would not be adversely affected, and the research could not be carried out without the waiver. However, in this example, the "minimal risk" question comes into play when considering if the device will alter the treatment decisions by the physician. If so, then this study would incur more than minimal risk and informed consent must be obtained. Furthermore, is there a detriment of asking patients to enroll in the study? For waiver of consent, the research could not be reasonably carried out without the waiver. Here the patient could be made aware and informed consent can be sought. In this example, there is nothing to lead us to believe the patients lack DMC, meaning informed consent should be sought, and the treatment device could alter the decision of the physician representing more than minimal risk, and for both of these reasons informed consent should not be waived.

As Emergency Medicine research moves forward over the next decade, the questions of minimal risk, EFIC, and waiver of informed consent should be explored to determine what standards work best balancing the protection of our patients while achieving better outcome measures and diagnostic accuracy.

12.5. **Research funding and conflicts of interest**

Objectives:

1. To describe ethical issues related to commercial funding of research.
2. Describe what types of bias industry will place on research
3. How, if at all, does publication bias play a role in research?
4. To understand the importance of delineating data ownership prior to data collection

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12.5.1 Case Study

A study is published in a peer reviewed emergency medicine journal on the ability of a device to obtain access in patients quickly. The company who partially funded the study asks that the study be repeated, which they will fully fund the study, and ask that more focus be given to the direction of their patent. The research will pay for a research coordinator who is already on your staff for an additional year and you will have full control of the data but the company will have editing rights.

12.5.1 Study Questions

1. Should emergency medicine researchers participate in research that is funded by industry?
2. What clarifications need to occur prior to instituting collaboration with industry?
3. How can conflict of interest affect data collection and subsequent publications?

Background Information:

External funding represents a vast resource to expand our ability to further science in collaboration with industry. As our funding models are changing from governmental grants to foundations, pharmaceutical and bioengineering firms, our ethical and moral obligations must stay true. It is the responsibility of the investigator, to the best of their ability, to publish the data truthfully, whether positive or negative. In essence the principal investigator should focus on the conduct and process of the study, and not the outcome, to achieve the most unbiased results possible.

Data obtained should be as unbiased as possible, and all funding sources, and potential conflicts of interest must be declared to the journal editors and the readers. To minimize conflicts of interest, research in emergency medicine should be conducted with emergency researchers directing or assisting in all phases of the research design, data

collection, data analysis, and dissemination of results. Emergency physician involvement helps to ensure that research conducted in the emergency department and out-of-hospital settings is reported in a manner that is accurate, unbiased, and contextually appropriate. Additionally, prior to the start of any study where there is collaboration with industry, there needs to be written agreement of who will maintain the data, initiation of data collection, agreements between investigators and industry sponsors.

In the case presented above, the conflict of interest is financial. The investigator would have the appearance of bias as this further grant would pay for other projects and resources that may not be available otherwise. If we assume that the first study was of sound work and was of sufficient size to prove any benefit or detriment, it would appear that any additional work only would confound or discredit the prior work. This problem is frequently encountered in industry-sponsored work. One study found that up to a third of all randomized control trials sponsored by industry used selective reporting of the results where positive results were published more frequently than negative. (Hopewell et al) Review of the literature has focused on the amount of positively favored works published in the literature and the lack of negative result publications. The principal investigator must realize the sources of bias and be aware of them as they will be ever present and cannot be removed.

Balance can be achieved in research with the investigators, industry, and the study populations. The equipoise lies with the principal investigator, who cannot remove all sources of bias but can be aware of them and confront them, while focusing on the integrity of the study and not solely looking at outcomes. Submission of all data outcomes needs to occur to change positively favorite publication bias. Whether the peer reviewer industry will follow has yet to be determined but with such scrutiny of publication bias, it is up to the researchers to achieve true neutrality.

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