



Ethical and Regulatory Issues in Clinical Research

Syllabus (2 credits)

Course Director: Ana S. Iltis, Ph.D.

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This course prepares clinical researchers to critically evaluate ethical and regulatory issues in clinical research. The principal goals of this course are to prepare clinical researchers to identify ethical issues in clinical research and the situational factors that give rise to them, to identify ethics and compliance resources, and to foster ethical problem-solving skills. The course aims to deliver practical guidance for investigators through discussion of critical areas of clinical research ethics. An additional aim of the course is to enable participants to recognize the different ways in which research participants may be vulnerable and the ethical issues raised by including and excluding vulnerable participants. By the end of the course, participants will:

- Understand the regulatory framework that governs human subjects research and the distinction between compliance and ethics
- Be able to identify major ethical concerns in the conduct of clinical research, including situational factors that may give rise to ethical concerns
- Be able to apply an ethical problem-solving model in clinical research

Faculty

Laura Bierut, MD, Professor of Psychiatry

John Chibnall, PhD, Professor, Department of Neurology and Psychiatry, Saint Louis University

Rebecca Dresser, JD, Daniel Noyes Kirby Professor of Law

James M. DuBois, PhD, D Sc, Hubert Mäder Endowed Chair and Department Chair, Department of Health Care Ethics, Saint Louis University

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David M. Jaffe, MD, Dana Brown/St. Louis Children's Hospital Professor of Pediatrics and Director Division of Emergency Medicine

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Catherine Woodstock Striley, PhD, MSW, LCSW, ACSW, MPE, Research Instructor
Associate Director, Master of Psychiatric Epidemiology Program

Teaching Assistant

Andrew Plunk, MPH, Research Assistant, Center for Clinical Research Ethics

Assignments and Assessments

Participants will be assigned articles to read for each class session. Cases to be discussed in class are included in the syllabus to facilitate class participation. A scenario-based instrument will be given at the start of the first day of class and on the last day of class, using different scenarios. This is to aid the instructor in evaluating the course.

Three forms of assessment will be used in this course:

- Participation in class on a weekly basis, including meaningful participation in the case discussions, is required. Participants will be assigned to a group. These groups will meet during class time to discuss assigned cases. Ordinarily, groups will be responsible for reporting to the whole class the nature of their discussion and recommendations. Cases are provided in the syllabus (see below). Please notify the instructor as soon as possible if you will miss class. Participants who are unable to attend a class session should view the recorded session. (See below for further information on missed sessions.)
- Reflection questions: Each week, participants will be required to submit via email to the course master and teaching assistant a 1-2 page written response to *one* of the reflection questions provided on the week's topic. Participants choose which question to answer.
- Participants will write a case analysis, using a model taught during the first class day, of a case of their choice. Cases may be drawn from personal experience or identified from other sources (such as on-line case libraries). The instructor will provide guidance on identifying appropriate cases. The case analysis must be turned in by May 1, 2009. The instructor will read and comment on a draft of each participant's case analysis for anyone who would like to submit a draft. Drafts must be received no later than April 17, 2009. Alternatively, participants may choose to analyze one of the cases assigned for in-class discussion *as long as the draft (if desired) and final case analysis are received prior to the class day on which the case will be discussed.*

The course will be graded on a scale of A-F, with pluses and minuses used at the instructor's discretion. Attendance, class participation, and completion of all assignments will be required to pass the course.

All classes will be recorded. Students who miss a class should watch the digital archive of the class or turn in a written response to two 'reflection questions' (instead of only one) for the class they missed. Attendance and participation will account for 50% of the grade and written assignments will account for 50% of the grade.

Course Schedule

The course will meet for a total of 12 two-hour sessions. Dates for class meetings are listed below.

January 12, 2009: Ethical Decision-Making: Research Ethics and Compliance (Iltis)

Preliminary assessment

Regulatory and compliance issues in human subjects research

Human subjects research ethics

Framework for ethical decision-making

The following resources will be distributed during week one and posted online:

Emanuel, Ezekiel, David Wendler, Christine Grady (2000). 'What makes clinical research ethical?' JAMA 283(20): 2701-2711.

DuBois, James M. 'A framework for analyzing ethics cases,'
<http://www.emhr.net/framework%20for%20analyzing%20ethics%20cases.pdf>

DuBois, James M. 'Justifying decisions when values clash,'
<http://www.emhr.net/justifying%20decisions%20when%20values%20clash.pdf>

Koppelman, Elyssa. 'Explanation of federal regulations for human subjects research,' parts 1 and 2. (<http://www.onlineethics.org/CMS/research/modindex/resethpages/reghum.aspx> and <http://www.onlineethics.org/cms/13123.aspx>)

Cases: (for in-class discussion)

Case 1 (by Ana Iltis): Family members living in a household with an individual who has a diagnosis of bipolar but who is not being managed medically are recruited to participate in alternate family therapy models. The family members, but not the person with the bipolar diagnosis, will be enrolled in the study. The family members will participate in family therapy sessions. Some families will participate in family therapy sessions modeled on one approach to therapy and others will have sessions following a different model of therapy. Family members will be asked questions individually and collectively at the start of the study and then once a month during the study about: the impact on their lives and on family dynamics of living with a person with unmanaged bipolar disorder, the strategies they use to cope in their household, and the ways in which they attempt to convince the person with the bipolar diagnosis to seek and adhere to treatment. As part of the sessions, families will be taught different coping and communication methods and different ways of encouraging the person with bipolar disorder to seek and adhere to treatment will be discussed. Family members will be encouraged to apply those methods and then report back on the results. The study will explore both how family therapy affects family members of persons with unmanaged bipolar disorder and whether they are able to become effective in encouraging the person with bipolar disorder to seek and adhere to treatment. Participation in the study is expected to last one year.

- **What would you say to this study if you were reviewing it on an IRB?**
- **What questions, if any, would you ask of investigators? What changes, if any, would you request?**
- **Would it change anything if the person with unmanaged bipolar was a child? A teenager? A person with mental retardation? If so, how would it change your opinion and why? If not, why not?**

Case 2 (by Emily Anderson; based on a case in Kimberly Hoagwood, Peter S. Jensen, and Celia B. Fisher, *Ethical Issues in Mental Health Research with Children and Adolescents*, Lawrence Erlbaum, 1996; www.emhr.net): The positive effect of lithium in the treatment of children and adolescents with aggressive behavior has been proven through clinical investigation. However, no published studies have included children with mental retardation. Investigators plan to conduct a two-arm parallel group study at a residential treatment facility for persons with mental retardation. Participants will be randomized to treatment with lithium or placebo. Many staff members at the treatment facility have already been using lithium to treat aggressive behavior of

persons with mental retardation. The institutional review board (IRB) approved the study, but many staff members continue to believe that using placebo would be withholding of an effective, established treatment.

- **What ethical concerns does the case raise?**
- **What issues and practices should the IRB have considered prior to approval?**
- **Did the IRB act appropriately in approving this study? Why or why not?**
- **What safeguards should be put into place in conducting the study?**

January 26, 2009: Research Environment and the Ethical Conduct of Research: Conflicts of Interest or Commitment (DuBois)

Reading Assignment:

Dana, Jason and G. Loewenstein (2003). '[A social science perspective on gifts to physicians from industry](#),' *JAMA* 290(2): 252-255.

Levinsky, Norman (2002). '[Nonfinancial conflicts of interest in research](#),' *NEJM* 347(10): 759-761.

Bekelman, Justin et al (2003). '[Scope and impact of financial conflicts of interest in biomedical research: a systematic review](#),' *JAMA* 289(4): 454-465.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on January 26, 2009

1. What are the major categories of conflict of interest or commitment in research?
2. Why do we worry about conflicts of interest or commitment? Which types of conflicts are more worrisome and which are less worrisome? Why?

Cases for in-class discussion

Case 1 (from [Responsible Conduct of Research](#) by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, p. 138): A tissue collection and storage company has signed a contract with a medical school to collect human tissue for research purposes. The company plans to collect tissues from healthy and unhealthy human donors at the medical school. Tissue donors will sign an informed consent for giving the company their tissue. They will not receive money for their tissue but will be informed that their tissue may benefit other people. Once the tissue is donated, it will be placed in a tissue bank. All personal identifiers linking the tissue to the donor will be removed. The company expects to profit by charging access to its tissue database. It also plans to patent valuable cell lines. The medical school will receive a portion of the profits.

- **Do you see any ethical problems with this proposal?**

Case 2 (from 'The Dual Role of the Clinical Investigator,' Online Ethics Center for Engineering, 9/9/2006. National Academy of Engineering:

www.onlineethics.dnsalias.com/CMS/research/modindex/resethpages/dual.aspx): You are a psychiatrist and your patient, Ms. Kay, has been enrolled in a research study that you are conducting involving a new antipsychotic drug. She enrolled in hopes of finding a medication that did not have the side-effects of her previous medication. Ms Kay is now six days into the study following a wash-out period of her previous psychotropic. She is now becoming quite agitated and you fear that she may decompensate. You find that despite displaying some symptoms of her psychosis, she speaks coherently about the issue of medication selection. As her clinician you hoped that you could find her a medication that would not have the side effects that she finds so burdensome with her previous medication. You try to talk to Ms. Kay about your concern that the new medication may not have had time to take full effect and may prove better for her, if given that time, but she does not seem to understand that point and only insists that she now feels terrible, much worse than she used to feel on her previous antipsychotic and “wants out.” You are also concerned that the new drug may be proving ineffective or having worse side-effects for this patient and if so, and you insist, it will greatly damage her trust of you. As the lead investigator for this study, you hate to see any patient drop out before this new drug has had time to take full effect. The drug promises to be an important clinical advance in clinical treatment, especially if you can better identify the profile of patients with which it works best.

- **How do you manage your dual responsibilities as clinician and as investigator in this case?**
- **Should the patient’s treatment be based on what is best for them or what is best for the research?**
- **Should a long-term clinician be allowed to be the investigator with their own patient? Why or why not?**
- **Are there circumstances in which the clinician/investigator would not produce conflict?**

Case 3 (from Responsible Conduct of Research by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, p. 162): A clinical researcher receives \$3,200 per patient from a drug company to enroll patients in a clinical trial of a new hypertension medication. The money covers patient care costs and administrative costs for the duration of the study and includes a \$200 finder’s fee. After the initial screening and enrollment, patients will make a total of eleven 15-minute office visits during the study. At each visit, nurses will take blood, record vital signs, and ask questions about their hypertension. The clinician will do a physical exam.

- **Is this financial arrangement a COI or apparent COI?**
- **Should it be prohibited? Why or why not?**
- **During the informed consent process, should patients be told about the clinician’s financial interests? How much detail should they be given?**

February 2, 2009: Informed Consent and Voluntariness (Iltis)

Reading Assignments:

Robert J. Levine (2001). ‘Consent issues in human research,’ in *Encyclopedia of Bioethics*, Vol. 5, Stephen G. Post, 3rd ed, NY: Macmillan Reference, pp. 1280-1290.

Paul S. Appelbaum, Loren Roth, Charles Lidz, Paul Benson, and William Winslade (1987). 'False hopes and best data: Consent to research and the therapeutic misconception,' *Hastings Center Report* 17(2): 20-24.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu. Responses should be received by 1 p.m. on February 2, 2009

1. Why does informed consent matter in research? Is it ever appropriate not to seek the consent of subjects? Why or why not?
2. What are the necessary conditions for free and informed consent? How does the therapeutic misconception relate to the necessary conditions for free and informed consent? What concerns do you have about the informed consent of patients who have no viable treatment options outside of research?
3. Is the therapeutic misconception sufficiently harmful that must be avoided at all costs? Why or why not?
4. Do you think the therapeutic misconception would be greatly reduced if patients did not enroll in studies conducted by their own physicians? If so, would you support a rule prohibiting physicians from enrolling their own patients? What concerns would you have about such a proposal?

Cases for in-class discussion

Case 1 (from Responsible Conduct of Research by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, pp. 208-9): An announcement in the newspaper and radio encourages people to enroll in research protocols to test a new anti-flu medication. The announcement emphasizes that subjects will receive a free physical exam, free health care for 60 days, and \$400 compensation. The new drug is very promising in either stopping the full-blown symptoms of the flu or preventing it altogether. The protocol has already been approved by an IRB.

- **What questions would you ask if you were a potential subject?**
- **Should the IRB have approved the protocol? Why?**
- **What safeguards could be put into place to protect voluntariness?**

Case 2 (by Ana Iltis): University Hospital has a well-respected ENT department; several of the physicians in the department have partnered with medical device companies over the years to develop improved hearing aids. Dr. Jones presents a proposal to the IRB to conduct a study sponsored by a corporation to study a new implantable hearing aid that is not visible when implanted. Subjects will not be charged for the device but will be responsible for all costs associated with the surgery and maintenance of the device. If a subject has difficulty with the device or for any reason is not satisfied, the subject will be responsible for all costs associated with removing the device. Subjects will also be responsible for the approximately \$1200 cost of replacing the battery every 12-14 months. The study is expected to last three years.

- **What concerns does this proposal raise?**
- **What options does the IRB have regarding the protocol?**

- **What changes, if any, should the IRB require?**
- **What information should be given to potential subjects and how?**
- **What are the advantages and disadvantages to approving such study?**

Case 3 (by Emily Anderson and James DuBois; www.emhr.net): Dr. Jones has received funding to develop and test an intervention to prevent child abuse among pregnant women in outpatient drug treatment programs. Many current and recovering substance-abusing women are at risk for abusing their children due to difficult life circumstances and lack of personal and financial resources needed to cope with the demands of a young child.

Prior research has identified economic and psychosocial factors associated with child maltreatment, including personal childhood experiences of maltreatment, poor mental and physical health, lack of social support, limited education, and limited knowledge of infant development. Yet, little research has been done to determine whether child abuse rates can be decreased through intervention programs with mothers being treated for substance abuse. Dr. Jones plans to use the Parenting Stress Index and test of knowledge of child development to identify mothers who are at risk of abusing their children. Those who are at risk would then be randomized to receive either social work visits alone or the experimental intervention involving counseling, a brief education program on child development, and regular social work visits. After six months control group participants would receive the full experimental treatment. The social work visits would have two purposes: (1) to provide additional resources tailored to the participants' needs, and (2) to look for signs of child abuse and neglect in the home. The dependent variables are: (1) predictors of risk (i.e., scores on the Parenting Stress Index and knowledge of child development), and (2) signs of child abuse and neglect.

Dr. Jones mentions in her proposal to the IRB that participants will be told that the study is a services program designed to improve parenting skills but their data might be used in a quality assurance study. She does not want to inform them of the purpose of the study for fear that they would decline to participate out of fear that their children could be taken away and because labeling them as "at risk of abusing their children" is stigmatizing. She argues that the risks of non-disclosure are far outweighed by the potential benefits to children.

- **Should the investigator be allowed to withhold the study purpose? Why or why not?**
- **If so, what protections should be in place? Why?**

February 9, 2009: Decision-Making Capacity and Vulnerable Research Participants (DuBois)

Reading Assignment:

Kipnis, K. (2001). '[Vulnerability in research subjects: A bioethical taxonomy](#),' *Ethical and Policy Issues in Research Involving Human Participants*, Volume II. Bethesda: National Bioethics Advisory Commission: G-1-G-13.

DuBois, James M. (2007). '[Decision-Making Capacity and the Involvement of Surrogates](#),' in *Ethics in Mental Health Research*. NY: Oxford, pp. 77-91.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu. Responses should be received by 1 p.m. on February 9, 2009

1. What problems does Kipnis identify in the current approach to the protection of vulnerable groups? What approach does his taxonomy of vulnerability recommend? What concerns or problems do you see with such an approach?
2. What concerns emerge when members of vulnerable populations are included in or excluded from a study? What role should surrogates play in making research participation decisions?
3. What types of protections might one encourage or require investigators to offer to subjects with different types of vulnerability described by Kipnis and others? To what extent should the costs of offering such protections be considered a legitimate reason to exclude vulnerable persons?
4. Why do we have special concern with the enrollment of vulnerable subjects? Should vulnerable subjects routinely be excluded from research participation? If not, are there circumstances in which they should be excluded?
5. What concerns emerge when persons who are cognitively impaired or are mentally ill are included in and excluded from research?
6. Should the level of decision making capacity persons must demonstrate to be allowed to enroll themselves in a clinical trial vary based on the level of risk posed by a study?

Cases for In-Class Discussion: Decision making capacity

Case 1 (by Angela Dunn and James DuBois; www.emhr.net): Bernadette is a 78-year-old woman who was recently diagnosed with Alzheimer's disease. Prior to her diagnosis, she had retired from a 40-year career as psychiatric researcher at a prestigious university. Her work primarily focused on dementia related disorders of the elderly, including Alzheimer's.

Her doctor has submitted a research proposal, which would investigate the effects of an experimental drug, Huperzine, on persons with late-stage Alzheimer's. This drug inhibits the breakdown of specific neurotransmitters and stimulates neurotransmitter regeneration. In Phase II of the drug trial, 40% of the research subjects experienced seizures with temporary but prolonged motor function loss. Bernadette's doctor would like to enroll her into the study. Although treatment will begin in late stage Alzheimer's, Bernadette is at an early stage in the disease so is apparently able to express her wishes for treatment. Having been a psychiatric researcher for many years, she certainly exhibits an understanding and appreciation of her disorder. When the benefits and side effects of Huperzine are presented to her she shrugs and says, "If I couldn't find a cure for Alzheimer's then I might as well help someone else find it." So Bernadette signs the informed consent form, allowing the researchers to administer Huperzine to her long after her cognitive capacities have been seriously impaired. Once Bernadette reaches the advanced stages of the disease, Huperzine is administered and she experiences the described side effects. Her distraught family members learn of the study and immediately file a grievance with the hospital's Institutional Review Board. Her family questions her capacity to make decisions about her future when she initially signed the consent form. They contend that Bernadette would never have wanted to be subjected to such treatment.

- **As a member of the hospital's IRB, how would you respond to the grievance? What would you do?**
- **Should the IRB have approved this design? Why or why not?**

Case 2 (loosely based on the AbioCor artificial heart trials. See: Morreim, E. Haavi (2006). 'End-stage heart disease, high-risk research, and competence to consent,' *Perspectives in Biology and Medicine* 49(1): 19-34): NuCardio has developed a totally implantable artificial heart intended as a permanent replacement for a human heart; it is to be used in lieu of a heart transplant. The FDA requires that this investigational device be studied only in patients in end-stage biventricular heart failure who have a life expectancy of less than 30 days, have failed all existing therapies and are not eligible for transplantation.

- **What ethical concerns do you have about conducting this type of study in this population?**
- **Should such a study be approved? Should there be special conditions on enrollment into the study or protections for participants?**

Case 3 (from: James DuBois (2007). *Ethics in Mental Health Research*. NY: Oxford, pp. 91-92): Twenty years ago, Roger was diagnosed with schizophrenia, paranoid type. Over the years, he has undergone many types of treatment with varying degrees of success. Roger found that although the treatments reduced his symptoms, often the side effects were more than he could bear. So he would take himself off medication, and his schizophrenic episodes would return. At times, Roger is so worn out by frightening all-night psychotic episodes that he considers suicide; but he still resists going back on medication.

Lately, Roger has been feeling a lot better. He hasn't had an episode in a month and his mind feels "clear." He has even been able to work on the next chapters of his mystery novel, which he had abandoned months ago when his episodes were particularly intense. Roger's mother, whom he visits regularly, notices his improvement and is delighted. However, they both know that it is only a matter of time before the symptoms return and the disorder consumes his life again.

Willing to try anything to avoid another episode, Roger decides to visit a psychic to get "advice from the heavens." His mother is not particularly bothered by Roger's visits to psychics. She's glad he's trying to find some source of hope. Upon visiting an astrologer, he is advised to seek out an experimental drug and is assured that the "universe will grant him a miracle cure" through this new medicine. Roger leaves the astrologer and heads to the local diner to read the newspaper. On the back page, he reads about a Phase II clinical trial of an antipsychotic agent that is enrolling adult patients with schizophrenia.

Roger immediately contacts the research director at the university-affiliated hospital. The researcher explains that this experimental drug is being tested for its efficacy and safety and might not improve his symptoms. The drug has shown modest success in previous trials but has potentially severe side effects. Roger expresses extreme interest in participating.

The research protocol involves administering a short assessment of decision-making capacity to all potential participants who are interested in the project. Those who are deemed incompetent are either not allowed to participate or need the permission of a legally authorized surrogate decision maker in addition to providing their own assent. Among other things, the assessment explores understanding of the protocol, appreciation of risks and benefits, and the reasoning process used to decide whether to enroll. The evaluator finds that Roger is not in a psychotic

episode and that he understands the risks and benefits extremely well. But he is concerned when Roger explains that he is certain he will receive benefits from the study and that he decided to enroll because an astrologer instructed him to seek out this study.

- **Should Roger be enrolled in the study, and if so, what procedure should be used?**

February 16, 2009: Phase One Studies and Translational Science Research (Dresser)

Reading Assignment:

Wood, Alastair and Darbyshire, Janet (2006). '[Injury to research volunteers – the clinical-research nightmare](#),' *N Engl J Med* 354(18): 1869-1879.

Agrawal, Manish and Ezekiel Emanuel (2003). '[Ethics of phase 1 oncology studies](#),' *JAMA* 290(8): 1075-1082.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on February 16, 2009

1. What is the primary purpose of phase 1 clinical trials?
2. What criteria should govern the decision to move from “bench to bedside”?
3. What ethical considerations should determine whether a phase I study population is composed of healthy volunteers, or of patients?
4. What are the major ethical issues associated with phase I oncology trials?

Cases for In-Class Discussion

Case 1 (from Stephen Post (2006). 'Gene therapy for Alzheimer's Disease,' Online Ethics Center for Engineering, National Academy of Engineering): Basal forebrain cholinergic neurons deteriorate severely in AD. Nerve growth factor (NGF) prevents deterioration of these neurons in mice, rats, and large primates. When administered to aged rats with lesions in the basal forebrain, NGF actually reverses memory deficits. By gene therapy, aged primates show a reversal of deterioration of cholinergic neurons. The effects of NFG have been widely replicated but never applied to humans before gene therapy became available in the research context.

In this study, a Phase I safety trial of ex vivo NFG gene therapy is proposed. The AD patient's fibroblasts will be genetically modified (using virus vectors) to produce NFG in vitro and then grafted into the brain. Based on pre-clinical primate studies, five injections of cells will be performed on each side of the brain. Greater numbers of injection grafts might compromise safety, while fewer will likely prove inadequate.

Over the course of the year, post-operative patients/subjects will be monitored monthly for safety and for cognitive function using various cognitive scales as well as scales measuring activities of daily living. Because this protocol involves surgery and some risk, these patients/subjects will be in the early stages of AD so as to still be competent to provide informed consent. Additionally, early-stage patients/subjects have the most to gain by prevention of neuronal deterioration and improved function of remaining neurons. Each patient/subject will be accompanied to all clinic

visits by an informant (usually the primary family caregiver), who will also make daily observations for adverse events. A condition of entering this study is that current anti-dementia drugs like donepezil, which in some AD patients can mitigate certain symptoms like word finding difficulties and inattentiveness to tasks for a period of six months to a year, cannot be prescribed during the first year of the study.

- **Are people with Alzheimer's disease the appropriate population for this phase I study?**
- **Should people with early-stage AD be permitted to make independent decisions about participating in this study, or should investigators adopt another approach to study enrollment?**
- **Is there sufficient preclinical evidence to justify this study?**
- **Are the risks presented by this study ethically acceptable?**

Case 2 Duchenne muscular dystrophy is caused by an X-linked genetic mutation. Existing therapies can reduce symptoms, but there is no cure and most patients die by age 25. Scientists are developing an approach that would add genes for the muscle protein that is missing in muscular dystrophy patients. To deliver the genes, scientists insert them into genetically altered adeno-associated viruses.

Animal studies have had promising results and now researchers want to test the intervention in humans. They propose a phase I study that would enroll six participants between ages 10 and 21. Participants would receive two doses of the altered virus over a six-week period. The goal is to determine the maximum safe dose. Based on animal tests and human trials involving other genes and viral vectors, the risks include harmful immune response and possible cancer triggered by improper gene insertion. If the intervention appears safe, investigators will conduct later studies to assess its effectiveness. A consent form explaining the study is included below.

- **What ethical issues does this proposal present?**
- **What problems exist in assessing the risks for participants in this trial?**
- **Should minors be asked to participate in phase I trials?**
- **What comments would you make about the forms explaining the study to potential participants and parents?**



INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant _____ HRPO Approval Number _____

Principal Investigator _____ PI's Phone Number **(314)** _____
Last First Credentials

Title of Project: **Adeno-Associated Viral Insertion of Dystrophin Gene**

You are invited to take part in a research study by Dr. Smith and/or colleagues.
Please ask for an explanation of any words you do not understand.
You may want to talk about the study with your family or friends before you decide to be in it.

1. Why is this study being done?

Dr. Smith and his team need volunteers for this very important study to test whether a normal dystrophin gene can be safely introduced using a weakened virus for transport. If this normal gene can be inserted in a muscular dystrophy patient, it may replace the defective gene. This may lead to a new treatment for muscular dystrophy.

2. What am I being asked to do?

You will receive an injection under the skin in your arm on two occasions about six weeks apart. The injection contains live virus with the normal dystrophin gene. You will visit the doctor for physical examination and blood drawing once a month for the next six months after the injection. You will have two tablespoons of blood drawn at each visit. You will fill out a questionnaire at each visit. It takes about 30 minutes to fill out the questionnaire.

3. How long will I be in the study?

You will be in the study for about six months.

4. What are the Costs? None.

5. What are the Risks?

Likely: Pain and bruising at the site of injection and with blood-drawing
Less likely: Flu-like illness
Rare: Induction of malignancy or severe immune reaction

6. What happens if I am injured because I took part in this study?

Washington University investigators and their staffs will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study,

please contact the Investigator and/or the Human Research Protection Office Chairperson from Item 8. Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University.

7. **Are there Benefits to taking part in the study?** The study will produce important information about a potential new treatment for muscular dystrophy. We will learn if a normal dystrophin gene can be inserted by using the weakened virus as a vector.
8. **What other Options are there?** Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled. Other than not taking part in the research, you may continue care with your usual physician.

9. **What about Confidentiality?**

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study explained in this consent form.

10. **The research team will follow state and federal laws and may share your information with:**

- Government representatives, to complete federal or state responsibilities
- Hospital or University representatives, to complete Hospital or University responsibilities
- Your primary care physician if a medical condition that needs urgent attention is discovered

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer, at 1-866-747-4975.

11. **Who do I call if I have Questions or Problems?**

If you have any questions, concerns or complaints about the study, or feel that you are injured because of the study call Dr. Smith at 454-6000. If you wish to talk to someone else, or have questions or concerns about your rights as a research subject, call Dr. Philip Ludbrook, Chairman of the University's Human Research Protection Office, at (314) 633-7400 or (800) 438-0445.

12. The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate. For safety, it may be in your best interest to allow follow-up outside the study. The PI will share any new information that could change how you feel about continuing in the study.

13. Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

I have read this consent form and have been given the chance to ask questions. I will also be given a signed copy of this consent form for my records. I give my permission to participate in the research described above, *titled: Adeno-Associated Viral Insertion of Dystrophin Gene*

Participant's Signature or Legally Authorized Representative Date

Signature of person providing Informed Consent Date

Relationship to Participant

Thank you for your important contribution to research studies that are trying to improve medical care.

Case 3 In 2006, a German drug company called TeGenero and a Massachusetts-based company called Parexel International co-sponsored the first human trial of a monoclonal antibody, TGN1412. Researchers believe that this antibody could lead to improved treatments for leukemia and rheumatoid arthritis.

A division of Parexel International, the Clinical Pharmacology Research Unit (CPRU), recruited eight healthy men to participate in the trial. Six of them received TGN1412 and two received a placebo, an inactive agent. Every man receiving TGN1412 experienced serious adverse reactions. All were transferred to the facility's intensive care unit and two had to be placed on respirators to sustain their breathing.

All of the subjects are now expected to survive, but some may have lasting health problems due to their exposure to the study drug. As compensation for their time and trouble, subjects were offered \$4100. The study plan called for them to spend three nights in the research unit and to make 11 follow-up visits to evaluate the drug's effects.

The study is under investigation by the Medicines and Healthcare Products Regulatory Agency (MHRA), the British counterpart to the U.S. Food and Drug Administration. The MHRA's initial inquiry into the trial found no serious deviations from accepted standards for phase I human tests. The inquiry report said that the Parexel CPRU met recognized standards for clinical trial,

laboratory, and manufacturing procedures. It also said that data from a study of monkeys exposed to TGN1412 failed to suggest the possibility of serious adverse events in humans.

At the same time, critics cite several problems with the trial, including the dosage schedule for TGN1412. The drug was given to each of the six subjects over an hour-long period, rather than over a series of days. The latter approach would have allowed the first subjects to be closely monitored before the others received the drug. Some experts also said that the effects of TGN1412 could have been anticipated, based on laboratory data and the human response to drugs closely resembling TGN1412. One subject complained that he was not told that TGN1412 had never been given to humans before. He also said that at an orientation session on the trial, he was not given enough time to study the eleven-page consent form.

- **Should subjects be paid for participating in phase I trials?**
- **What measures should investigators adopt to reduce risks to subjects in phase I trials?**
- **What study information should phase I trial participants be given and how should it be delivered?**
- **Should subjects injured in phase I studies receive compensation for their injuries? If so, what should they receive?**

February 23, 2009: Randomized Controlled Trials and Placebo Controlled Trials (Shannon)

Reading Assignment:

Samuel Hellman and Debora S. Hellman (1991). '[Of mice but not men: Problems of the Randomized Clinical Trial](#),' *NEJM* 324: 1585-1589.

Robert Temple and Susan Ellenberg (2000). '[Placebo-controlled trials and active-control trials in the Evaluation of new treatments. Part 1: Ethical and scientific issues](#),' *Annals of Internal Medicine* 133: 455-463.

Ezekiel Emanuel and Franklin Miller (2000). '[The ethics of placebo-controlled trials – a middle ground](#),' *NEJM* 345: 915-919.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on February 23, 2009

1. Do researchers ever have a therapeutic obligation toward their subjects? If so, when and why? If not, why not?
2. If researchers do have a therapeutic obligation toward their subjects, may they ever conduct research on them? If so, when and why? If not, why not?
3. Is there an ethically relevant difference between conducting a placebo controlled drug trial and a placebo controlled surgical trial?

Cases for In-Class Discussion

Case 1 (from Timothy Murphy (2004). *Case Studies in Biomedical Research Ethics*. Cambridge: MIT Press, p. 33): In the late 1990s research showed that people with Parkinson's disease experienced shrinkage and disappearance of certain tissue in the brain. Parkinson's is a disease of the central nervous system that causes muscle rigidity, tremors, and balance problems. Symptoms can range from mild to very severe. Researchers were hopeful that transplantation of fetal tissue would be beneficial for people with very severe disease. The procedure would require opening the skull to transfer tissue to the desired location. Ordinarily, researchers test new innovations for safety and efficacy against existing treatments. Because no good treatments were available for severe Parkinson's, the researchers decided to use a control group. Half of the subjects would receive fetal tissue and the others would receive nothing. The researchers determined that it would be necessary to open the skull of all subjects, not just those who would receive the actual tissue, to account for the placebo effect. Patients in the control group were, therefore, taken into operating rooms and treated as if they were going to receive the tissue transfer. Some were asked, 'Are you ready for the implant now?' The patients then were anesthetized and their skulls were drilled as if for actual implantation. Later, they were told that they had not in fact received the tissue.

- **Is it acceptable for studies to have control groups that receive only placebos as long as subjects are told in advance that they might not receive the active agent?**
- **Was the use of placebo defensible in this study?**

Case 2 (Ana Illtis): Many patients experiencing psychiatric illness, especially depression and anxiety disorders, do not seek care from a mental health specialist. They seek routine health care from a primary care provider, such as an internist or family practitioner. There is evidence that these primary care providers often do not recognize these conditions and neither provide nor refer for appropriate treatment. A number of screening questionnaires have been developed and tested to aid primary care providers in detecting mental health concerns among their patients. Although there is evidence that the questionnaires help physicians effectively identify patients who may have certain common psychiatric conditions and decrease the incidence of suicide – particularly among the elderly, there is little evidence that physicians regularly use the questionnaires. Investigators design a randomized, controlled clinical trial to randomize four urban, four suburban, and four rural medical practices to one of four arms of a Randomized Controlled Trial (RCT). Each arm will have one urban, one suburban, and one rural practice. In the first arm, all physicians in the practice will participate in a 30 minute training session on the use of a screening questionnaire, the practice will be provided sufficient copies of the questionnaire to use with all patients over a three month period, and the screening questionnaire will be attached to the packet of papers patients are asked to complete when they arrive for their appointment. In the second arm, all physicians will participate in the 30 minute training session, the practice will receive sufficient copies of the questionnaire for use by all patients over a three month period, and physicians will receive weekly email reminders to use the questionnaires. In the third arm, the each practice will be provided with sufficient copies of the questionnaire to use with all patients over a three month period. The fourth arm will receive no intervention. At the end of the three month period, patient records from all 16 practices will be reviewed to determine the rate of use of the screening questionnaires, rate of detection of psychiatric conditions and rate

of treatment or referral of such patients. Any suicide attempts or incidents will be recorded. No names or other identifiers of patients or physicians will be recorded.

- **What ethical issues does randomizing medical practices raise?**
- **What are the risks of this study? How can they be minimized?**
- **Should this type of research be allowed? Encouraged?**

Case 3 (From: the March 2001 *ACP-ASIM Observer*, copyright © 2001 by the American College of Physicians-American Society of Internal Medicine. By David Cassarett, MD, Lois Snyder, JD, and Jason Karlawish): Drs. Smith and Jones, senior partners of Internal Medicine Associates, have never before done office-based industry-sponsored drug research. Recently, Dr. Brown from DrugCo invited them to serve as co-investigators in a randomized double-blind clinical trial of a new medication to treat type two diabetes. It is the last trial DrugCo needs to complete before applying for FDA review and approval of the drug. . . . Subjects who enroll will be randomly selected to receive either one or two doses of the new drug or a placebo for six months. . . . Subjects cannot take any other oral drugs for diabetes [during the study].

DrugCo will pay . . . for all study-related care. . . . Drs. Smith and Jones are definitely interested in office-based clinical research. They serve an urban population that includes many chronically ill, elderly and low-income patients. They believe that better data is needed to substantiate best practices for this population.

Moreover, the trial is attractive because it promises free medication, and so many of their patients have been hard hit by drug costs.

- **What are the advantages and disadvantages to this trial design?**
- **What concerns does the design raise? How can these concerns be minimized?**
- **Should the physicians in this case enroll their own patients in this study? What factors might be relevant to the decision to enroll a particular patient?**

March 2, 2009: Research on Children (Jaffe)

Reading Assignment:
[45CFR46 Subpart D](#)

Tauer, Carol (1994). 'The NIH Trials of Groth Hormone for Short Stature,' *IRB: A Review of Human Subjects Research*, 16(3): 1-9 [read excerpt included in Emanuel et al (eds.) *Ethical and Regulatory Aspects of Clinical Research*, 2003, Johns Hopkins University Press, pp. 240-247]

Freedman, Benjamin, Abraham Fuks, and Charles Weijer (1993). 'In loco parentis: Minimal risk as an ethical threshold for research upon children,' *Hastings Center Report* 23(2): 13-19. [read excerpt included in Emanuel et al (eds.) *Ethical and Regulatory Aspects of Clinical Research*, 2003, Johns Hopkins University Press, pp. 247-252]

Leikin, Sanford (1993). 'Minors' assent, consent or dissent to medical research,' *IRB: A Review of Human Subjects Research* 15(2): 1-7 [read excerpt included in Emanuel et al (eds.) *Ethical*

and Regulatory Aspects of Clinical Research, 2003, Johns Hopkins University Press, pp. 252-258]

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on March 2, 2009

1. Does the fact that pediatric research benefits children as a group necessarily justify inclusion of specific children in research? If so, why? If not, what additional conditions must be met to justify enrolling a particular child in a study?
2. Is there research that it might be permissible to conduct on minors who can give assent that would be inappropriate on children who cannot give assent?
3. Are there situations in which it is inappropriate to seek parental permission for a child's participation in research?
4. What unique ethical concerns emerge in pediatric research?

Cases for in-class discussion:

Case 1 (by Ana Iltis): Missy is a 9 year old girl diagnosed with ALL at age 6. Twenty months after her diagnosis, she is diagnosed with a combined bone marrow and extramedullary relapse. She undergoes hematopoietic stem cell transplantation and experiences a second remission. At ten months post-transplant, she again is diagnosed with a combined bone marrow and extramedullary relapse. Attempts at inducing remission fail and she is not a candidate for a second HSCT. Missy's parents meet with her oncologist, Dr. Jackson, to discuss Missy's treatment options. Dr. Jackson explains that there are no known cures for Missy's condition, but that she could enroll in a Phase 1 study of a new chemotherapeutic regimen that might help children like her in the future. Dr. Jackson explains that the primary purpose of the study is test the safety of the regimen for use in children. If enrolled, Missy will remain an inpatient at the children's hospital where she has received care over the last three years for much of the rest of her life. An end-of-life care plan will be developed regardless of whether Missy participates in the study. Missy's parents are enthusiastic about the study. They say that even though it's unlikely to help her, it might, and at least she will be well cared for by doctors and nurses they have come to know well and trust. They think it is important to help find a cure for children like Missy in the future. Dr. Jackson explains to the parents that Missy cannot be enrolled in the trial if she really doesn't want to be in it; participation requires her assent. Dr. Jackson and Missy's parents talk with her about the trial. Her parents strongly encourage Missy to be part of the trial, they tell her how important it is to help other children, they remind her that "you never know – this might be just the thing for you," and they tell her that she will be able to have the nurses she loves take care of her. They avoid talking to Missy about death, though several nurses, a social worker, and a psychologist all have told them repeatedly that Missy knows she is dying.

- **As an IRB member, how do you evaluate a protocol such as the one described above? Under what category of subpart D might such a study be approved and why?**
- **What do you think Dr. Jackson does well? What does Dr. Jackson do poorly?**

- **Do you have any concerns about Missy's ability to make a decision? Why or why not? If Missy does not want to be in the study, should her parents be allowed to enroll her? If Missy does want to enroll, are there any reasons that might lead us to worry about her decision? Do you think Missy's parents understand the situation sufficiently well to enroll her in the study?**

Case 2 (by Ana Iltis): The Infectious Disease department at the University is conducting an active-controlled trial of an influenza vaccine on children ages 8-16. The study will compare a standard influenza vaccine plus placebo with a new vaccine that includes an adjuvant believed to boost the efficacy of the influenza vaccine. The adjuvant influenza vaccine has been widely tested in adults and is believed to be both safe and effective. The study requires a screening visit, one vaccination visit, and two follow up visits that will involve blood draws. Subjects also must keep a symptom diary and report to the ID clinic any time they or someone in their household experiences flu-like symptoms. If the investigator determines that the subject's flu-like symptoms are sufficiently severe, the protocol will require an additional blood draw. Subjects and their parents together will be paid \$25 for each visit to the clinic. If a visit involves a vaccination or a blood draw, payment for the visit will be increased to \$35.

- **What concerns do you have about the risk to children in this study?**
- **What else would you like to know before evaluating the protocol and why?**
- **Should the dissent of children be respected? Why or why not? Should investigators be concerned with risks a child who dissents may face at home?**
- **Is it appropriate to pay parents and children? Why or why not?**

Case 3: (by Adrienne Carpenter; based on: Bainbridge, J. (2007). Gene therapy clinical trials for inherited eye disease. *Expert Review of Ophthalmology*, 2(4), 517-519.): Dr. Mays is a doctor of ophthalmology interested in the medical potential of gene transfer to treat Leber's congenital amaurosis (LCA). LCA is a degenerative retinal disorder. Patients have very poor vision at birth and can suffer a number of other effects from the condition. Dr. Mays is proposing a Phase I clinical trial using gene transfer to treat LCA. LCA is a particularly good candidate for gene transfer because of the location and type of genetic defect involved as well as the fact that the condition is degenerative and there is no known effective therapy.

Pre-clinical data suggest that the proposed transfer will likely be most--if not exclusively--effective in patients who have not yet experienced significant degeneration of the retina. Younger patients are the best candidates for the purpose of assessing efficacy. However, enrollment in the study would pose a significant risk, due to the novelty of the intervention. The study can be conducted on healthy adults, but they would very likely not benefit from the gene transfer, due to the advancement of retinal damage.

- **Who should be the first subjects in this research? Why? What factors should be considered in making this decision?**
- **When is it ethically justifiable to enroll children in research studies involving novel therapies or treatments? Is it ethical in this scenario?**

March 16, 2009: Selected Research Integrity Issues: Authorship and Peer Review (Striley)

Reading Assignment:

Welker, James and Jack McCue (2007). 'Authorship versus "credit" for participation in research: A case study of potential ethical dilemmas created by technical tools used by researchers and claims for authorship by their creators,' *Journal of the American Medical Informatics Association* 14(1): 16-18.

Shamoo, and David Resnik (2003). 'Collaboration in Research: Authorship, Resource Sharing, and Mentoring.' *Responsible Conduct of Research*. NY: Oxford University Press, pp. 48-59. (Please note that the full chapter is longer but the required reading is only pages 48-59)

Sismondo, Sergio (2007). 'Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry.' *PLoS Medicine* 4(9): 1429-1433.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on March 16, 2009

1. What are the standards for authorship and acknowledgement in your field?
2. What are the major concerns associated with ghost management or ghost authorship? How can these problems be avoided?

Cases for In-Class Discussion

Case 1 (from Caroline Whitbeck (2006) 'Confidentiality and data access,' Online Ethics Center for Engineering. National Academy of Engineering): A clinical psychologist –investigator, whom you know, did his own pilot study of psychiatric patients with certain characteristics. This work suggested interesting implications for your own studies, and you approached him about being a co-investigator on a new study. His role is to interview a certain population of patients and score them for certain characteristics. You agreed that you would be first author on any publications in your field, and he would be first author on any publications in clinical psychology. The work was completed several years ago and you published two articles in your field with yourself as first author. Your colleague has since taken on heavy administrative responsibilities and has yet not written anything and only was able to participate in commenting on one of the two articles you drafted and so was listed as an author only on that one. You are aware that, as PI for the grant that funded the work, you have responsibility to ensure confidentiality of patient data and are concerned that your collaborator has data of sensitive nature. Although your collaborator removed names, addresses and patient record numbers from the data, the interviews paint a detailed picture of the physical and mental condition of each patient, detail that the psychologist says he needs in writing up his own articles. Your colleague says that he does intend to publish based on his pilot study and your joint work, but he does not know when.

- **What, if anything, do you do now?**
- **What ethical issues arise from failure to publish findings?**

Case 2 (from Adil Shamoo and David Resnik (2003). *Responsible Conduct of Research*. NY: Oxford, p. 67): Dr. Thomas published a review article on recent developments in mitochondrial genetics. In the article, he mentioned his own work prominently but failed to mention the work of several other researchers who have made key contributions to the field. Dr. Thomas is clearly one of the most important researchers in the field, and he has done some important work. But he also has some long-running feuds with some of the other prominent researchers in the field, based in part on fundamental disagreements about the role of the mitochondrial DNA in human evolution. In his review article, in several instances he cited his own work instead of giving proper credit to colleagues who had published their articles before his.

- **Is this plagiarism?**
- **Is it unethical?**

Case 3 (by Ana Iltis): Dr. Jackson, an expert on attention deficit disorder in adults, is contacted by Educa, a medical communications company. Educa invites Dr. Jackson to share her expertise in the medical literature by writing an educational article summarizing research results concerning Fokus (a new medication being marketed for adults with ADD) that will help clinicians decide when to prescribe the medication. She also will write a letter to the editor responding to some recent studies that question the safety and efficacy of Fokus. Educa will provide editorial assistance for both pieces, and Dr. Jackson will be paid \$2500 for the article and \$1500 for the letter to the editor. Dr. Jackson clarifies with Educa that she will author the paper and letter herself. She signs a contract with Educa. Educa provides Dr. Jackson with an outline for the article and letter as well as a list of references. Educa also provides a list of key points to make in the article. The Educa representative tells her that they offer this service to leading experts whom they know are very busy to facilitate timely publication. Dr. Jackson submits her article and letter to Educa and receives an edited version back from the company. Educa has removed statements in the article referring to case reports of episodes of major depression in patients taking Fokus. Dr. Jackson questions the decision to remove these statements and the Educa representative working with her explains that these statements are likely to confuse clinicians and do not provide clear guidance on when and how to prescribe Fokus.

- **How should Dr. Jackson respond and why?**
- **What interest might Educa have in this particular medication? Where is Educa's funding coming from?**
- **What concerns do relationships such as that between Educa and Dr. Jackson pose for clinicians who rely on the medical literature?**

Case 4 (from Adil Shamoo and David Resnik (2003). *Responsible Conduct of Research*. NY: Oxford, p. 115): An Associate professor in a large university submitted a major grant proposal to the NIH. During the grant review at the study section, a reviewer noticed that the P-value calculated for the table was based on eight experiments. However, the methods section had stated that the experiments had been conducted four times in duplicate. A preliminary inquiry by the study section staff raised further questions about the authenticity of the data. The executive secretary of the study section felt compelled to write to the university's grant office for clarification, with a copy to the ORI. The university responded by conducting an inquiry. The faculty member admitted that she always uses the number of experiments times the number of

replicates to obtain the total number of experiments. The university chose not to proceed to the investigation. Instead, it warned her to stop using such methods. The university informed ORI of its decision.

- **What failed, and what preventive remedies you would recommend?**
- **Discuss the appropriateness of the university's action.**
- **Now that the case is in the ORI's hands, should it accept the university's decision?**

March 30, 2009: Selected Issues in Research Integrity: Data Management and Collaborative Research (Chibnall)

Reading Assignment:

Bird, Stephanie and Dave Housman (1995). 'Trust and the collection, selection, analysis and interpretation of data: A scientist's view,' *Science and Engineering Ethics* 1: 371-382.

Chalmers, Iain (1990). 'Underreporting research is scientific misconduct,' *JAMA* 263: 1405-1408.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on March 30, 2009

1. What are the major ethical issues surrounding data management that are likely to arise in your area of research?
2. Have you ever observed a situation in which you were concerned about data management issues? Think about how the situation was handled and what you believe should have been done differently.

Cases for In-Class Discussion

Case 1 (from Responsible Conduct of Research by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, p.157): A faculty member of a Midwestern university has a postdoctoral fellow who had been working for three years on one aspect of a new drug that has just been approved by the FDA. The drug company pays the mentor \$5,000 per year consulting fees. This year, the company is sponsoring a three-day conference in San Francisco, all expenses paid. The conference brings together approximately 15 scientists from around the country who are leaders in research on this drug. Their job is to speak to 300 invited guest physicians who are potential prescribers of the drug. All the physicians' expenses are paid. The speakers will each receive a \$3,000 honorarium. The faculty member accepts the invitation, and the postdoctoral fellow hears about it by accident. He informs his mentor that he has new data indicating that the drug may have serious side effects. The mentor points out that the work is not yet published and that she will deal only with the published data for now.

- **Does the faculty member have a conflict of interest? If so, what type of conflict of interest is it? Does anyone else in this case have a COI?**
- **What should the faculty member do?**
- **What should the postdoctoral fellow do?**

Case 2 (from Responsible Conduct of Research by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, p. 66): Dr. Watson and Dr. Gramm are developing a genetic test for adult-onset (type II) diabetes. Their assay tests for several thousand mutations that are strongly predictive of type II diabetes. Of those patients who test positive for these mutations, 60% will develop type II diabetes. Watson and Gramm hope that their test will be used on children and adolescents to provide information that may be helpful in preventing type II diabetes or managing its effects. If people learn early that they have these mutations, then they may be able to undertake a diet and exercise program to prevent this disease or prevent some of its devastating consequences, such as loss of limbs or blindness.

Watson and Gramm plan to patent the test when their work is complete. They have been collaborating with several researchers at other institutions, sharing data, reagents, methods, and so on. They recently received a request for some preliminary data from several colleagues, including their collaborators as well as other colleagues in the field.

- **Should they share their data?**
- **Would it make any difference if a private corporation funded their research?**

Case 3 (from Responsible Conduct of Research by Adil Shamoo and David Resnik; NY: Oxford University Press 2003, p. 113): A postdoctoral fellow published a paper on the fluorescence spectrum of a newly discovered compound bound to a fluorescent dye. The spectrum of this bound compound in experimental animals differed substantially from that of the control group. This was considered to be a significant finding and he published his results. Later, one of his colleagues informed the mentor that she had discovered the control animal experiments had never been conducted. She said that the postdoc had relied on her control data from previous studies. Furthermore, the colleague had spoken to the postdoctoral fellow, who had said that he thought that it was acceptable to use historical data, but admitted that he had not mentioned the source of the data in his paper.

- **Considering that the postdoctoral fellow says that he thought the use of historical data was acceptable, do you think that his behavior constituted misconduct? Is it viewed as misconduct by the definitions provided by federal government or your definition?**
- **Is the colleague obligated to tell the fellow of his decision to go to his mentor?**
- **Should the colleague have considered other alternatives rather than telling the mentor, for example, informing the appropriate university official and/or ORI or insisting that a correction be published?**
- **What alternatives does the mentor now have, and which one should she seriously consider?**
- **If you were the university official in charge of the research integrity program, would you be likely to send it to the inquiry stage?**

April 6, 2009: Research in Developing Nations (Manary)

Reading Assignment:

Levine, Robert J. (1999). 'The need to revise the Declaration of Helsinki,' *NEJM* 314(7): 531-534.

Brennan, Troyen (1999). 'Proposed revisions to the Declaration of Helsinki – Will they weaken the ethical principles underlying human research?' *NEJM* 341(7): 527-530.

Bhagwanjee, Satish et al (1997). 'Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study.' *BMJ* 314: 1077-1081 plus commentaries by Kale and Bhagwanjee et al that appear at 1081-1084.

FYI (not required reading, but informative)

'Informed consent in medical research.' Letters in *BMJ* 314: 1477-1483.

'Informed consent.' Letters in *BMJ* 315: 247-254.

'Ethics and international research.' Letters in *BMJ* 316: 625-627.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on April 6, 2009

1. Does the fact that subjects enrolled in the 076 regimen studies Levine discusses would not receive any treatment whatsoever if they were not in the study justify the use of the placebos?
2. What duty of care, if any, do investigators have toward research participants?
3. Are the ethical standards for research conducted in resource-poor settings the same or different as the standards for ethical research conducted in the United States?
4. Evaluate the decision not to obtain informed consent from the participants in the Bhagwanjee et al study.

Cases for In-Class Discussion

Case 1 (from 'Negotiating research practices with local communities,' Online Ethics Center for Engineering, National Academy of Engineering): As a genetic epidemiologist working with an isolated community of [people in a developing nation], you have identified an endemic mutation that seems to explain their group's high susceptibility to heart disease at a young age, which had hitherto been attributed to their diet. In meeting with the community's leadership to discuss these results, you encounter two reactions.

On the one hand, the leadership was relieved to learn that their high fat diet was now "proven" not to be the source of their problems. On the other hand, they now insisted that you not link this genetic finding with their community in any publications or reports, because they fear that a known genetic vulnerability would make their daughters less marriageable among neighboring groups.

- **How should you respond?**

Case 2 (from *Ethical Issues in International Biomedical Research*, edited by J. Lavery, C. Grady, E. Wahl, E. Emanuel. NY: Oxford, 2007. pp. 65-66): The Maria Luisa Ortez Women's Co-operative Health Center is a clinic for women in the small rural town of Mulukuku in central Nicaragua. It is a refuge for abused and battered women and their children and provides them with shelter and legal advice while working to help alleviate their physical, mental, and social distress.

Dental decay and its sequelae in children are issues of great concern to the leadership of the Cooperative, the director of the Women's Health Clinic and the mothers of the town of Mulukuku. The director of the clinic met a dental health researcher from the United States, and invited him to assess the extent of dental decay in the community and to help develop a solution. The researcher traveled to Mulukuku, examined a sample of primary school children, and suggested a study that would evaluate the effectiveness and sustainability of a primary oral-health training program. Together they designed a project to train local community health workers to apply fluoride varnish, extract teeth, and perform Atraumatic Restorative Technique (ART) fillings, which are relatively cheap and require little equipment other than hand instruments. After training local dentists, the researcher hoped to evaluate the quality of the fluoride varnish applications, the effectiveness of pain relief during tooth extractions, and effectiveness of the ART technique in reducing general pain and discomfort from the teeth. He was also interested in assessing the overall improvement in quality of life that could potentially result from the oral health program.

Local well water (the principal water source) was sampled and tested for fluoride content. These data were then analyzed to formulate an appropriate caries prevention strategy for the local community. The researcher held an initial meeting with community leaders to explain the project. The director of the clinic and the leaders of the Cooperative approved the study and granted the researcher permission to conduct the study in Mulukuku at the Maria Luisa Ortez Center. The IRB at the researcher's institution in the United States also approved the study as a pilot project. Focus group meetings with parents of young children were held to explain the study and to encourage wide community approval and participation. Because of the low literacy rates in the community, meetings were held for parents and children at local schools. Local health promoters facilitated discussions in Spanish, and decisions were documented by a show of hands. Parents gave consent for their children to participate in the oral screening exam and baseline quality of life assessment in this way.

- **Is this an acceptable method of obtaining consent? Why or why not?**

Case 3 (from *Ethical Issues in International Biomedical Research*, edited by J. Lavery, C. Grady, E. Wahl, E. Emanuel. NY: Oxford, 2007. pp. 264-266): Noma is an inflammatory disease that rapidly destroys both soft and hard tissues of the mouth and face, often resulting in severe disfigurement and even death. Noma now occurs predominantly in immunocompromised or chronically malnourished children in developing countries who have limited or no access to medical care. The disease is most common in areas where poverty, poor environmental

sanitation, poor oral health, unclean water, close residential exposure to livestock, and increased exposure to endemic viral, bacterial, and parasitic infections prevail. Studies in parts of rural Nigeria suggest that there may be as many as 10,000 cases of Noma in any given region of the country at a time. However, it has been extremely difficult to document and make valid epidemiological estimates of the disease in Nigeria, since it affects children in the most remote and impoverished areas of the country where there is limited health care infrastructure. Also, little is known about the pathophysiology of the disease. Acute necrotizing gingivitis (ANG) is considered one of the precursors of Noma, but only a small percentage of children affected with ANG progress to a full manifestation of the disease, and the precise mechanism remains elusive.

An international team of investigators proposed an epidemiological study of Noma in carefully selected, socioeconomically deprived Nigerian communities where the disease was frequently encountered. The epidemiological research focused on collecting data about the environment, lifestyles in the communities, sanitation, food and water quality, and residential proximity to livestock and other domestic animals. This international collaborative study aimed to generate knowledge to help elucidate the relationship between Noma and ANG.

Investigators hypothesized that the mechanism for Noma is related to protein-energy malnutrition (PEM). They postulated that (1) the stress of PEM, a condition usually complicated by concurrent deficiencies of certain specific micronutrients, such as retinol, ascorbate, folate, zinc, and iron not only favors differential overgrowth of some pathogenic oral microorganisms but also impairs oral mucosal immunity; (2) malnutrition, microorganisms related to poor hygiene, and other factors associated with immune suppression distinguish individuals who develop Noma and/or ANG from those who do not; (3) malnutrition can alter the genotype and/or pathogenicity of some microorganisms related to Noma, including viruses that impair immune function; and (4) the occurrence of Noma is related to hygiene and contamination from livestock.

A large-scale epidemiological survey of rural communities was conducted using a survey developed by the World Health Organization. Preexisting data were used to identify nutritionally deprived areas where the prevalence of the disease was reported to be the highest, and from these areas, communities were randomly selected to participate in the survey. In each area, researchers surveyed villagers with questionnaires and clinical survey methods. In addition, blood samples, anthropometric measurements, and information on medical and environmental factors were collected from children with active Noma.

From these communities, 180 children with PEM were randomly selected to take part in a cross-sectional, case-control study of Noma pathogenesis. The case group had 60 children who had Noma, but not ANG. The 1st control group had 60 children, matched for age, gender, and ethnicity. These children had ANG, but they did not have Noma. The 2nd control group had 60 children, also matched for age, gender, and ethnicity, who had neither ANG nor Noma.

After researchers obtained informed consent from the child's parent or guardian, each child had a complete history and physical exam, blood collected, and detailed information about habits and social environment was recorded. Children were screened for HIV-1 and HIV-2, and those found positive were excluded from the study. Results of the test were given to the child's parents or

guardian through the study pediatrician, and the child was referred to government HIV clinics. For the study, the child's name, gender, address, parents' names and occupation, number of siblings and other pertinent demographic data, including residential proximity to livestock, particularly goats, rams, and cattle, were recorded for each child. Questions relating to nutrition and dietary habits, health behavior, and other health problems that might have a bearing on the efficacy of a prevention strategy were also included. Detailed information was obtained about each child's medical history and recent history of illnesses, particularly eruptive fevers and dietary habits. Those requiring treatment for Noma were referred to government clinics, or the Noma specialty hospital, whether or not they were enrolled in the study.

The consent conversation took place with the children and their parents or guardian in the presence of a 'neutral' primary health care nurse; this individual, familiar with the language and local traditions, was not employed by the state or the research team. The study was explained and the adults were invited to ask questions for further clarification before signing the consent form. Many of the parents signed with thumbprints and some requested the nurse to sign for them. In all cases, the child's dissent and/or lack of cooperation prevailed over parental permission.

- **Compare this case to #2. Individual consent was sought, but were the measures taken sufficient?**
- **Does the presence of a 'neutral', uncompensated third party safeguard informed consent? Why? Why not?**

April 20, 2009: Research on Animals (Dresser)

Reading Assignment:

Adil Shamoo and David Resnik (2003). 'The use of animals in research,' in *Responsible Conduct of Research*. NY: Oxford, pp. 214-229.

Kopelman, Elyssa. 'Federal Regulations for Animal Research.' Available online at: <http://www.onlineethics.org/cms/16217.aspx>

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on April 20, 2009

1. What are some of the major ethical principles governing the use of animals in research? What criteria must be met for animal research to be ethical?
2. What are the major ethical justifications for using animals in research?
3. Does the permissibility of a study ever depend on the kind of animals involved? Why or why not?
4. What is an example of a study that would be unethical if conducted in humans but ethical if conducted in animals?

Cases for In-Class Discussion

Case 1 (from 'Unexpected Adverse Events,' Online Ethics Center for Engineering, 2006, National Academy of Engineering Accessed: Saturday, August 25, 2007)

www.onlineethics.dnsalias.com/CMS/research/modindex/resetpages/adverse.aspx): Christopher Adams is just beginning his first totally independent research project as an Assistant Professor at a large biomedical research institution. This project is an outgrowth of the work he did as a postdoc. The project will examine the comparative efficacy and safety of two different types of bone implants with regard to their capacity to promote the healing of fractures. The study will be carried out in dogs.

Dr. Adams has submitted a protocol review form to the Institutional Animal Care and Use Committee (IACUC) and has obtained IACUC approval of the study. Twenty dogs are randomly assigned to either Group 1 or Group 2 and implanted with one of two devices. After eight weeks, the dogs will be sacrificed and the bones will be tested.

At six weeks, several animals in Group 2 die. The cause of death is unknown, but the animals appear anxious and uncomfortable at the time of death. The time course of the experiment is almost up, and Dr. Adams wants to continue with the hope that at least some of the animals in Group 2 will live to eight weeks.

As an alternative, he is considering sacrificing all animals at six weeks.

- **What should Dr. Adams do? Why?**

Case 2 (from 'Experiment Discomfort,' Online Ethics Center for Engineering, 2006, National Academy of Engineering, Accessed: Saturday, August 25, 2007 <www.onlineethics.dnsalias.com/CMS/research/modindex/resetpages/disan.aspx): You are a graduate student whose dissertation requires that you explore the workings of the central nervous system. Impressed with your ideas, your advisor proposes that the two of you apply for funding in order to perform experiments on an animal to find the information you need. You know that performing these experiments requires a fully functioning animal with a working nervous system - in other words, the animal must be conscious. You also know what such an experiment might be like. You know that the experimental procedure would begin with the administration of anesthetic, not for the animals' benefit, but for experimental convenience: it is much easier to handle the animals initially if they are rendered temporarily unconscious. You also know that there is no cheaper or more effective anesthetic than carbon dioxide, which works simply by cutting off the animal's oxygen supply. The animals would struggle violently when placed in gas chambers constructed for this purpose, until the oxygen content in their tissues drops below the level necessary to support consciousness. After rendering the animal unconscious, you would have to perform gross surgery, working quickly to restrain the animal and remove its limbs preventing further struggle that might result in nerve damage during the finer surgery to come. The finer surgery would take about an hour and a half. Although the animal need not be conscious during this period, exposure to carbon dioxide for such a long period would either kill the animal or cause irreversible brain damage, both unacceptable outcomes. Therefore, it would have to be allowed to regain consciousness during the finer surgery. By the time the animal awakes, its legs would be gone. The animal would likely explore the proximal stumps that remain after limb removal with its mouth and start to shake a little after exploring the wound sites, probably from shock. After the finer surgery and with its head braced, the animal, reduced to an experimental prep, would be subjected to intra-cellular penetrations of interneurons in its

central nervous system in order to explore the relationship between nerve cell activity and animal behavior. The final phase of the experiment can last another eight hours if the animal survives that long. All of these procedures are performed without pain killers in a fully conscious animal.

- **How would you respond to your advisor's request? Why?**
- **What, if any, difference does it make what kind of animal this is, and why?**

Case 3 (from 'A Question of Sacrifice,' Online Ethics Center for Engineering, 2006, National Academy of Engineering Accessed: Saturday, August 25, 2007

www.onlineethics.dnsalias.com/CMS/research/modindex/resethpages/neuroan.aspx): Eric Rosenthal is a second year graduate student in a neurosciences program. Having just completed his course work, he must design his own project of research. His special area of interest is in studying the effects of methamphetamine and related compounds on brain activity. These compounds are commonly abused as recreational drugs and, although many are illegal, new "designer drugs" or slightly different chemical variations, are developed on a regular basis by illicit drug manufacturers.

One of his first considerations in designing his project is to find an appropriate animal model. In his review of the literature, Eric finds that cats are an adequate model because their brains are physiologically and anatomically similar to those of humans. Rhesus monkeys, however, have brains even closer to those of humans with more complex patterns of brain wave activity. His protocol would entail restraining the animal, hooking up electrodes, measuring brain activity both before and after administration of the drug, then sacrificing the animal to examine any physiological and anatomical changes in the brain tissue.

Eric is concerned that any sedatives, anesthetics, or analgesics administered before sacrificing the animal could possibly alter the brain chemistry and consequently Eric's results. Yet, as a humane and compassionate person, he is concerned that the animals not experience any unnecessary pain or suffering.

Eric wishes to use the best model for his experiment, but hesitates to do so in this instance for a number of reasons. First, rhesus monkeys are much more expensive and less available than cats.* Second, Eric feels a certain "kinship" toward primates that he does not feel towards cats.

- **Are either of these issues appropriate considerations in selecting his animal model?**

The initial phase of the study, restraint and brain wave monitoring is not painful for the animal, though the animal will generally resist the limitations on its physical movement. Nonetheless, Eric believes that not providing any pain-reducing substances at this point is entirely appropriate. He is less certain when it comes to sacrificing the animal.

- **Are there humane ways to sacrifice the animal without providing anesthetics or analgesics?**
- **How might Eric deal with this issue?**

Assume that for purposes of Eric's study, it is not necessary to sacrifice the animal in the end. The protocol, which then only entails restraint and attachment of electrodes and administration of the drug under study, is rather noninvasive.

- **Is it appropriate to use the animals (either cats or monkeys) for other, unrelated experimental procedures afterward? What if the initial experiment involved a surgery from which the animal would survive?**
- **Should the availability or species of the animal weigh in this decision?**

** This scenario was adapted from one given by the AAMC*

April 27, 2009 – Research on Stored Human Biological Materials (Bierut)

Reading Assignment:

Kapp, Marshall (2008). 'Biobanking human biological materials,' Pharm Med 2008; 22 (2): 75-84.

Reflection Questions: Submit your response to one of these questions to: iltisas@slu.edu and aplunk@slu.edu Responses should be received by 1 p.m. on March 9, 2009

1. What are the major ethical issues encountered by researchers who want to use stored samples for research?
2. Who should control access to stored samples and the type of research that can be conducted using those samples? Why?
3. What kind of information should patients undergoing clinical procedures that will result in samples that can be stored be given as part of their informed consent process? Why? What options should they be given regarding storage of specimens? Why?
4. Is it ethically different to use samples originally collected for clinical purposes in research than to use samples originally collected for research in future research?

Cases for in-class discussion

Case 1 (from Weir and Ollick, 2004, *The Stored Tissue Issue*, pp. 6-7) The National Health and Nutrition Examination Study (NHANES) "was a three-part series of medical and epidemiologic studies carried out by the Centers for Disease Control and Prevention (CDC): Since 1966, more than 85,000 persons have participated in the studies. All the medical and health data [collected as part of NHANES III, which took place from 1988-1994] were linked to other personal information to facilitate the multiple purposes of the study and to make long-term follow-up more valuable. By the mid-1990s, CDC scientists had also produced an archive of approximately 19,500 blood samples stored in liquefied nitrogen and immortalized cell lines from approximately 8,500 participants.

To meet the ethical and legal requirements for informed consent, the NHANES III administrators, working with the IRB at the CDC, initially prepared a very detailed and technical statement on consent to be given to prospective participants in the study. Later judged to be too technically difficult, the document was replaced by a simple six-page booklet with descriptive text and

pictures about NHANES III. The only language in the booklet pertaining to informed consent for banked samples is a one-sentence, descriptive statement: ‘A small sample of your blood will be kept in long-term storage for future testing.’

The language of ‘DNA banking’ was hardly commonplace at the time of this study. Few participants would have had reason to ask the CDC physicians, nurses and scientists about that sentence. Yet some CDC investigators were subsequently bothered by an important ethical problem. On the one hand, they possessed what they described as an invaluable ‘national treasure chest’ of health information on a cross-section of the U.S. population and an unmatched archive of nationally representative DNA samples for biomedical research. On the other hand, they became concerned about the paucity of information they had provided the NHANES III Participants about the possible research uses of their stored blood samples. The consent document had seemed satisfactory when it was developed in the 1980s. But [it did not seem acceptable] for molecular research with DNA samples in the 1990s.”

- **Is the earlier consent sufficient? Does being “informed” change over time?**
- **How long do researchers remain obligated to participants? Until the end of the study? Until researcher or participant die? Is there an obligation to participants’ offspring?**

Case 2 (by Thomas Murray, ‘Interpreting consent for research on archived tissue,’ Online Ethics Center for Engineering): “A researcher believes that breast cancer occurs only when a combination of inherited and acquired genetic mutations occur, and theorizes that biopsied breast cancer tissue might be used to detect earlier pre-cancerous mutations that might help predict who is at increased risk of cancer. The scientist wants to use archived tissue samples and correlate them with later medical records indicating whether the person went on to develop breast cancer. The scientist wants to know whether certain early mutations are especially likely to predict later cancers, or alternatively whether the sheer number of mutations in key sites in the genome might be used as an index of risk.

Given the latency of breast cancer, the scientist prefers tissue at least ten to thirty years old, for which there is accurate and complete medical follow up. Unfortunately, at the time the tissues were obtained, informed consent for their use in research was either not asked at all, or was obtained through a very brief and general consent form. Neither researchers nor patients anticipated this kind of research when the tissues were gathered.”

- **Is the fact that the tissue itself was obtained with consent sufficient to pursue this research?**
- **If there was consent to store the tissue and use it for (unspecified) future research, is it permissible to treat that consent as authorizing this research?**
- **Is informed consent necessary for use of stored samples? Should it be? Why or why not?**
- **Should investigators attempt to identify the persons whose tissue is in question and seek consent? What are some reasons for and against this approach?**

Case 3 (by Caroline Whitbeck, ‘A question of host factors in side effects of medication,’ Online Ethics Center for Engineering, 9/10/2006): You are doing research to look for side effects of a certain drug. You know that evidence of such side effects shows up in blood. You also know that studies should be designed in a way that exposes subjects as minimal risk as possible. Given this, you designed a study which looks at blood already being drawn from patients for other purposes. As your study progresses, you discern that the pattern of both the efficacy of the drug and the incidence of some side effects suggests that they depend on genetic factors in subjects.

- **How, if at all, would it be ethical for you to look into this possibility?**

Case 4 (Source: ‘Recontacting old research subjects with new clinical findings,’ Online Ethics Center for Engineering, 9/10/2006): “Ten years ago, you began an ongoing study of the genetics of Hirschsprung Disease, a congenital condition of the colon which causes severe constipation or intestinal obstruction in children. You had already identified mutations on a gene that encodes a protein relevant to this disease in Amish families, and are now broadening your research to explore their association.

To conduct this study, families of patients with Hirschsprung Disease have been recruited through a support group newsletter. Responding families are asked to complete a family history and medical questionnaire, and families with multiple affected members are asked to donate a sample of blood for DNA analysis from both parents, affected and unaffected siblings

Meanwhile, a second laboratory showed that in some families, Hirschsprung Disease is associated with mutations in a second, unrelated gene called RET. RET is a proto-oncogene already known to cause a highly penetrant, dominant, familial thyroid cancer syndrome called, multiple endocrine neoplasia type 2A (MEN2A). Prophylactic thyroidectomy is sometimes undertaken in patients known to carry this gene, although it is not a sure prophylaxis, since other parts of the endocrine system can also be affected. In this light, you begin to screen the stored DNA samples from your Hirschsprung families for the RET gene mutations as well as your candidate gene.

One family consisted of parents with no history of Hirschsprung Disease, their affected three year old daughter and her unaffected one year old sister when you enrolled them in 1990. DNA re-analysis revealed a new mutation in the affected sibling’s RET gene, a mutation which has been associated with MEN2A. Another family joined the study in 1992. At that time, the family consisted of parents with no history of Hirschsprung Disease, two affected sons (fifteen and twenty years old), and a twenty-three year old unaffected son. Re-analysis of the family’s DNA revealed a mutation in the RET gene, not only in the two affected sons but also in their father.

- **You are a bench molecular biologist, not a clinical oncologist. What should you do with this information?**
- **In the first family, the subject at risk is still a minor. Is it appropriate to reveal her risk for an adult onset disease at this time? Would it be acceptable to disclose it to the subject’s treating physician?**
- **All the children in the second family are now adults, and are approaching the high risk age for the oncological manifestations of MEN2A. Do you have an obligation to**

contact these individuals and warn them of the cancer risks they now appear to face, even though you discovered these risks by conducting research they did not explicitly consent to?

- **Would it satisfy your responsibility to these families to simply notify the Hirschsprung Disease support group of this new association and urge them to encourage their member families to get tested by bona fide cancer geneticists for RET mutations?**

Additional Resources: The materials listed below are not required reading for this course. They are included here to identify readings on topics that may be of interest to some participants. Readings will be available in the same format as all other class readings.

Research on Pregnant Women, Embryos, and Fetuses

Ad Hoc Group of Consultants to the Advisory Committee to the Director, NIH. (1994). Selections from the Report of the Human Embryo Research Panel, Volume 1. Bethesda, MD: NIH. (Executive Summary ix-xx and Steinbock pp. 27-32)

Chervenak, Frank and Laurence McCullough (2003). 'An ethical framework for fetal research,' *Lahey Clinic* 10(1).

ACOG (1999). 'Ethical considerations in research involving pregnant women,' *Women's Health Issues* 9(4): 194-197.

45CFR46 Subpart B

Research Involving Prisoners

45CFR46 Subpart C

Gostin, L. (2007). 'Biomedical research involving prisoners: Ethical values and legal regulation,' *JAMA* 297(7): 737-740.

Lerner, B.H. (2007). 'Subjects or objects? Prisoners and human experimentation. *NEJM* 356(18): 1806-1807.

Sham Procedures in Research

Hong, S. and F. Miller (2003). 'Ethical framework for the use of sham procedures in clinical trials,' *Critical Care Medicine* 31(3): S126-S130.

Quality Improvement/Quality Assurance

Lynn, J. (2004). 'When does quality improvement count as research? Human subject protection and theories of knowledge,' *Qual. Saf. Health Care* 13: 67-70.

Lo, B. (2003). 'Oversight of quality improvement,' *Archives of Internal Medicine* 163: 1481-1486.

Rie, M.A. (1997). 'Rationing critical care services in the U.S.,' *Current Opinions in Critical Care* 3: 329-333.

Translational Research

Sugarman, J and G. McKenna (2003). 'Ethical hurdles for translational research,' *Radiation Research* 160: 1-4.

Public Health Research

MacQueen, K. and J. Buehler (2004) 'Ethics, Practice, and Research in Public Health,' *American Journal of Public Health* 94: 928-931.

Susser, M., Z. Stein, J. Kline (1978). Ethics in epidemiology, *Annals of the American Academy of Political and Social Science*, 437: 128-141.

Coughlin, S. (2000). 'Ethics in epidemiology at the end of the 20th century,' *Epidemiologic Reviews* 22(1): 169-175.

Weed, D. (2004). 'Precaution, prevention, and public health ethics,' *Journal of Medicine and Philosophy* 29(3): 313-332.