

Chapter 3: Ethics and Study Design

A. Introductory

Clinical research can be defined more or less broadly. For our purposes we define it to be any study that requires IRB approval. These include:

- a. Data from living individuals
- b. Biological material from living individuals
- c. Interaction or intervention with a living individual
- d. Use of a non-FDA approved, drug, device or biological

Such research includes:

- a. Physiological or behavioral studies of normal individuals or those with a specific condition.
- b. Review of data from large populations (Health Services Research) or from selected populations (chart review)
- c. Epidemiological studies of populations with or without an intervention.
- d. The study of human tissue either fresh or from repositories such as Banks or Pathology departments
- e. Interventional studies

Types of studies include

Phase 1: Toxicity (small number of individuals)

Phase 2: Efficacy, may include pharmacodynamics (small number of individuals)

Many studies are mixed Phase 1 and 2.

Phase 3: Efficacy and safety of unapproved drug, device or biological (tend to be large studies)

Phase 4: Efficacy and safety of approved drugs, devices or biologicals, or a comparison between interventions.

Each of these types of study requires the appropriate design to reach scientifically sound conclusions while protecting the participants and their identifiable human information.

A. Ethical Design

In clinical research, ethical science requires quality science. Although this may be morally obvious, it's also important practically because of the huge investments in money, effort, and personal risk and discomfort that the sponsor, investigators and the participants make. But poorly designed and

executed studies are frequently reported and can even influence practice and policy development. Among elements that make for poor and therefore unethical science are excessive risks compared to benefits, inadequate power, inappropriate allocation of dosages in comparison trials, poor selection and misallocation of participants, midstream changes of protocol, and failure to either monitor or record significant adverse events.

An important part of research integrity is the analysis of data. It's critical to recognize the importance of appropriate statistical analysis. Statistical approaches should be developed as part of the study design. If possible, hypotheses should be well defined in advance. Current statistical packages permit the mining of entire databases to identify statistically significant results that were not anticipated. The role of such findings continues to be subject to debate. Post-hoc reasoning should be employed only to generate new hypotheses and experiments, not to resurrect a failed investigation.

In therapeutic studies, both efficacy of the interventions and their safety are generally studied simultaneously but the design may focus on one or the other.

C. Appropriate risk to benefit ratio

Risk is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study. Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.

The federal regulations define only “minimal risk.”

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

[45 CFR 46.102(i)]

Risk above this standard is more than minimal (moderate, maximal) and that imposes limitations on the conduct of the research and increases the requirements for monitoring. It also requires more stringent approval processes when studying children or otherwise vulnerable populations. Increased risk should be accompanied by the probability of appropriately increased benefits.

Benefit applies to the potential of the research treatment to ameliorate a condition or treat a disease. This can apply to an individual participant or to a population. In research as in clinical medicine, results cannot be

guaranteed but, as a consequence of prior work, a benefit may appear to be a reasonable expectation. Since this is research, an advantage for the treatment groups cannot be presupposed. Since the risks have not been fully evaluated, a statement of individual benefit should be made most cautiously if at all. The investigator should always distinguish between research and treatment and never lure the patient into participating in hopes of remission or cure.

A main role of IRBs is to determine the risk versus benefit ratio for clinical studies. They must make sure that the physical risk is not disproportionate to the benefits. When the physical risk is minimal they must determine that psychological and social risks such as stigma are not important. It is not ethical to conduct a study in which an individual or a group is labeled so as to be stigmatized or to be made less employable or insurable.

Power can be defined as the adequacy of the number of research participants (treatment and controls) to confidently achieve or rule out statistically significant results for its principal end point. Estimation of power should always allow for dropouts and recruitment difficulties. Problems with recruitment and retention of participants to completion of the study impair power, sometimes making an investigation hopelessly biased or useless. A particular problem is the pursuit of subset analyses under conditions where the main result is negative. The subsets may not have enough power for a sound conclusion.

Normal Controls are research participants who do not have the condition under study. In physiological and behavioral interventions they undergo the same protocol as the participants with the condition under study in order to compare the two responses. Subjecting them to any significant risk may be inappropriate. However, Phase 1 clinical trials may be carried out in small numbers of normal control subjects who should be sure to understand the significant risks of the intervention.

Controls are research participants who receive an inactive treatment. In most trials they are selected by computer lottery from the group of eligible candidates with the condition under study.

Historical controls are subjects from prior studies or observational investigations whose data are compared with those of the current participants. Historical controls were used for years in clinical research and are still sometimes employed because they do not require additional data collection and risk. They often produce biases because the research population rarely duplicates the historical population.

Blinding refers to a process whereby the participant does not know whether he/she is receiving an active agent or a similar appearing inactive substance or mock procedure. Blinding is also used in research to refer to investigators who analyze components of a study such as X-rays or EKGs without knowing the identity and treatment of the participant. “The X-rays were read blind.”

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

Sometimes the effects of the agent in question are so obvious that true blinding is impossible. For example, if a weight loss drug were immediately effective, then the results would be obvious to everyone. Under those circumstances special attention has to be given to unbiased evaluation of adverse events, and conflicts of interest (see below) must be avoided.

Equipose

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

1. The individual investigator has genuine uncertainty regarding the comparative therapeutic merits of each arm, or
2. The medical community has genuine uncertainty regarding the comparative therapeutic merits of each arm.

Arguments have been made that true equipose rarely exists because previous research, whether it be in cells or animals or in small groups of humans, usually suggests that the proposed treatment has a better than 50% chance of being effective. In fact, those sponsoring clinical trials have to invest so much money and effort that they would hardly take the risk of such an undertaking unless they felt that the evidence supporting the efficacy of the intervention was reasonably strong. The FDA would not permit a Phase 3 trial unless the preliminary evidence was promising.

Use of Placebos

A placebo is an inactive version of a treatment identical in appearance to the real thing. Sometimes part of the treatment consists of active medications and part is placebo.

Once you recognize the need for controls then the question of whether placebo controls are desirable or acceptable must be answered. This has become a major issue because of international research (see below), in which it became apparent that placebos were being used when, in the developed world standard therapies were available and routinely utilized. The most recent version of the Declaration of Helsinki states:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote:

Footnote: The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or**
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.**

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

The issue of placebo controls also applies to studies in developed countries where the cost of studies using standard therapy in the controls is much greater and the end points much less definitive than in the use of placebo controls.

Standard of Care:

This term applies to the expected care in the medical community as a whole. Often, standard of care can be defined on the basis of practice guidelines, which are being developed by all medical specialties, element by element. The issue of standard of care becomes problematic when a study is to be performed in a developing country where it is impossible to provide medical care at anywhere near the level available in the developed world. The current expectation is that controls will be treated at the level of the Western standard of care, not the indigenous standard.

B. Selection of subject populations

Selection of the appropriate participant population plays a critical role in the experimental design. They must be selected and dealt with on the basis of the three principles of Human Research, Autonomy, Beneficence and Justice.

Autonomy

Autonomy is understood to mean that becoming a research subject is a totally voluntary act. Individuals must be solicited without coercion or even implied coercion. Individuals must be fully informed and understand what they are signing up for. IRBs require that the prospective participants understand a long list of things before they can sign a consent document. If the study requires a vulnerable population to be studied, (children, cognitively impaired) then a surrogate who, presumably, has their best interests at heart (parent for child, relative for the patient with Alzheimer's disease) must sign for the participant.

Individuals under the age of 18 are given special protections; so many studies pertain to adults only. The rule of autonomy requires that individuals are able to provide informed consent. Those who can't are afforded increased protections. When possible therefore, consenting adults are used. Age, degree of severity of the condition, life expectancy, ability to reach the study location and other factors may be included.

Carrying out research on special populations

It is essential to be able to conduct research on people who for one reason or another are vulnerable. This includes children who react differently to drugs than adults and for whom much too little research is carried out. This is due both to restrictive laws that limit the risks of research on children, parental fears for their children's well being and the need for written assent on the part of children over the age of 10 in addition to parental consent. The Pediatric Community needs to come together to decide what procedures carry minimal risk for children.

Participation of patients with serious emotional or mental problems in research related to their conditions is essential to bringing about therapeutic improvement. Tests have been developed to help determine whether an individual with such a problem is capable of providing informed consent.

Beneficence

Beneficence means that the intention of the research is for good. Beneficence is demonstrated in the risk-benefit analysis carried out by the PI and by the IRB. Of course many studies offer no personal benefit to the participants, and for these, great care must be taken that the risks are minimized.

Justice

Justice relates to access to research of all relevant populations specifically including age, ethnicity, gender and preexisting conditions. The federal government has made it clear that studies should try to include ethnic groups and women in proportion to the population in the community unless there is a good scientific reason not to (for example studying hypertension in African Americans). Issues that must be considered in justice determinations include:

Socioeconomic Status

Gender,

Race,

Age,

Existing medical conditions

Vulnerable populations (as noted above)

Determining ability to consent

Ensuring understanding of protocol

Appropriate surrogate for consent

Coercive nature of relationship (prisoners)

The need to use such populations must be justified

Cases:Chapter 3

Case: Depression

Jones agreed to join an ongoing sponsored clinical trial of an investigational new agent for treatment of severe unipolar depression, directed toward persons over age 55, to include at least 40% above age 70. Previous clinical trials with this agent have studied younger persons. This drug differs from others in that it is supposed to increase limbic serotonin levels and receptors markedly and rapidly, thus relieving an entire depressive episode in two days. The drug, when administered long-term, has been shown to increase limbic system serotonin receptors as demonstrated by PET scanning.

Jones was invited to participate because of her interest in clinical investigation, expertise in depression, and patient base as director of the hospital's in-patient depression unit, where she cares for the most severe cases including numerous suicide attempt survivors.

The study requires that patients be severely depressed and not suffer from a chronic medical condition. The acute study will compare the new agent with established drug therapy over a three-day period. Progress will be measured using depression instruments, serotonin and serotonin metabolite measurements, as well as PET scans on day zero and three. Following the acute trial, the participants will

be treated for depression free of charge for 1 year either with the new agent or a standard regimen and will have quarterly clinic follow-ups.

Participants will receive a payment of \$200 at the end of hospitalization, and \$50 plus transportation for each of the quarterly follow-ups.

Informed consent will be obtained on admission.

The anticipated adverse events from studies in other subjects are limited to nausea, dizziness and thirst, never serious in the younger populations previously treated.

A corporate Data and Safety Monitoring Board will monitor the study. The study will be carried out under the auspices of the GCRC but within the locked psychiatric ward, mainly on patients admitted under a 72-hour hold.

- A. Critique this study as though you are an IRB member, assessing the various review elements.
- B. Provide constructive suggestions as to how it may be improved to be more acceptable as a human subjects study.

After discussion and a number of revisions the IRB finally approves the protocol.

Jones undertakes the study and finds that recruitment is slow, with only 30% of eligible patients willing to participate. While the trial coordinator doesn't mention it, the Research Subject Advocate for the GCRC finds that those participants who improve clinically become progressively more reluctant to participate and have to be cajoled to continue. A subset of the subjects become

agitated and some sign out against medical advice as soon as their 72-hour hold is lifted.

Alarmed, Jones asks to break the randomization code and the company representative indicates that hers is the only site that has requested a code break. They reluctantly break the randomization and find that only subjects taking the experimental drug abandon the study. Jones believes, on the basis of personal experience with the patients that the drug effectively alleviates depression rapidly.

C. As a member of the Data and Safety Monitoring Board, write a detailed justified recommendation to Jones about the continued conduct of this study.

Case: Participant Rights

As a Principal Investigator of a major longitudinal observational study of the biological changes anteceding menopause, you are assigned the task of determining what information from the multitude of tests run to tell the individual about and how to go about the process. You have two principles to consider:

1. Will revealing information change behavior and thus alter the results of the study?
2. Do the participants, deserving of respect, have a right to know about any information learned about them so they can use it to better their lives?

The study will collect among other things:

Study

Body-mass index (BMI)

TSH

Fasting blood sugar

Depression rating scale

Clinical Relevance

Obesity

Metabolic Syndrome

Hyper or hypothyroidism

Glucose intolerance or diabetes

Depression

Blood pressure	Hypertension
MRI of brain	Tumors Anomalies Atrophy Multiple sclerosis
DEXA scan of spine and hip	Osteoporosis
Serum Lipids (APO E₄)	Hypercholesterolemia Risk for Alzheimer's Coeliac disease
Carotid artery ultrasound	Degree of atherosclerosis
Genotype	Many risks over time

Many of these studies will be analyzed and reported long after the encounter with the participant.

How should the study deal with abnormalities in these results and how should the issue be presented to the participants? A significant number of the participants have no personal physician. How should that situation be handled?

Case: Hepatitis Vaccine and the Military

Hepatitis E is a relatively uncommon form of hepatitis that is usually transmitted by exposure to the blood of persons with conditions like hepatitis B and C. Hepatitis E is not tested for in blood donations. There is reason to be concerned that military personnel, at time of war when injuries requiring transfusions are being suffered daily, that hepatitis E could result in substantial long term morbidity (illness).

A vaccine was recently developed for hepatitis E that required testing. When it was mentioned at an international military training program that this new vaccine was imminent and a clinical trial needed to be done, a senior officer in the Nepalese army volunteered the entire army in exchange for a donation of military supplies. The US Army was delighted to follow up on this.

As the director of this research program for the US Army, you are designated to arrange and perform this trial.

Questions:

1. What ethical considerations are paramount to you in designing this study?
2. Is there additional information you would like to have before you agree to this study?

Case: Prepubertal Girls

An investigator proposes to study the effects of dietary restriction and feeding on hormones related to metabolism and reproduction to learn more about the conditions conducive to the onset of menstrual periods in girls.

The proposed subjects are healthy girls between 8 and 12 years of age who have not had menarche but who are beginning pubertal development by Tanner Score.

The participants would be volunteers with parental consent admitted to the GCRC for 15 days full time during their summer vacation. They would have a 50 cc phlebotomy, be put on an optimal diet for three days, have another 50 cc of blood drawn, be switched to a diet with the same amount of protein but ½ the calories for six days have a third blood draw and then be returned to the optimal diet for six days and have a fourth 50 cc phlebotomy at completion.

The children would be given a gift certificate for \$100.00 at Borders at completion of the study.

You are the IRB member assigned to this protocol. You are very supportive of clinical research.

Questions:

- 1. Is this an appropriate experimental design?**
- 2. Is there a problem with consent?**
- 3. Is there an issue with blood?**
- 4. Is there an issue with the gift certificate?**
- 5. Is there an issue with HIPAA?**

Case: Teenage subject

Narrator: Dr. Smith, a pediatric diabetologist conceived of an amino acid infusion to accelerate recovery in diabetic ketoacidosis DKA, the most serious emergency associated with childhood diabetes. She got the sterile solutions produced and an IND (investigational new drug) permission to try it from the FDA as well as approval from her local IRB. To show results, the amino acid infusion must begin within four hours of starting the insulin infusion and Dr. Smith makes arrangements for the Pediatric Intensive Care Unit nurses to call her whenever a patient is admitted with DKA. Dr. Smith has a lot at stake in this study. If it works, a company is ready to prepare and market the amino acid solution, giving her and her institution a substantial financial shot in the arm.

Scene 1: Dr. Smith's bedroom.

She and her husband are sound asleep. Her pager goes off when the clock reads 2:20 AM. She rouses, turns it off and hears a disgusted groan from her husband. Again!, he complains. She picks up the phone and dials. It's the head nurse in the PICU.

PICU nurse: We just admitted Janey again in flagrant DKA. Do you know her, the fifteen-year-old who is always getting into trouble with her diabetes? She resents the condition, her family, and about everything else. You might want to ask her and her mother about participating in your study. In fact, I can get them to sign up and give the infusion so you won't have to come in.

Dr. Smith: Janey's my clinic patient and I know all about her. She is one of those teenagers who need to grow up, but at the rate she's going she might not live to be an adult.

PICU Nurse: Well, do you want me to get things going?

Dr. Smith: No, I had better go in. An MD on the protocol must do the consent and the assent. I'll be there in 45 minutes. Meanwhile just keep the regular treatment going.

Narrator: Scene 2: The PICU.

Dr. Smith and Mrs Granger are standing by a hospital bed in which lies Janey Granger hooked up to monitoring equipment and a couple of IVs.

Mrs. Granger: [Steps up to Dr. Smith and grabs her hand.] We are so grateful to you, Dr. Smith for trying to take such good care of Janey, but she got upset again and skipped her insulin for a few days, at least. [wringing her hands]. I can't really watch her every minute and she insists that she is grown up and knows exactly what to do about the diabetes.

Dr. Smith: [turning to Janey] Janey, I'm glad you realized that you were out of control and came in here. Your treatment seems to be going well up to now.

Janey: This sucks Doc. I can't do anything I want because of this miserable diabetes and my Mom keeps bugging me and worrying all day long. I wish she would leave me alone.

Dr. Smith: The important thing now is that you're getting better.

[turning back to the mother] **Mrs. Granger, there is something that I would like to ask you about.** [She pulls two folders out of her attaché case]

I am conducting a study about a special IV medication that is intended to safely decrease the length of time DKA needs to be treated. I have the consent form here that I would like you to go through carefully and then discuss with me. Since Janey is only 15, you have to give permission for her to be involved in the study.

Mrs Granger: Just show me where to sign. I know that you will do nothing to harm Janey. She really loves you and we are so grateful to you for caring for her, even through all her lapses.

Dr. Smith: You have to understand. This is a research study and the goal of the research is not to help Janey, but rather to determine whether or not this IV treatment improves the management of DKA for others down the line.

Mrs. Granger: Maybe, but you wouldn't give Janey anything that might harm her, so where can I sign?

Dr. Smith: No! [not quite losing her cool] We don't understand all the consequences of giving this IV or we wouldn't have to do a study. This is research! [Dr. Smith notices that Janey is listening very carefully to the conversation, still speaking to Mrs. Granger] While you go through the material in the consent form, I am going to talk to Janey and ask her for her assent. [turning to Janey]

Janey, I think you heard what your mother and I have been discussing. Do you have any questions about the research? You know it will involve just adding another IV to your current ones. It doesn't even require an additional stick.

Janey: Doc, I like you. But I'm feeling better and I want to get out of here as soon as possible. My mother is only thinking about herself. No one cares what I think! Why did you explain everything to my Mom first when I'm the one who's going to be the guinea pig?

Dr. Smith: You have a really good point there, Janey. I should have talked to you first, but your Mom has to give permission because you're a minor. What we would do is add an extra

infusion to what you're already receiving but it won't add to your time here. It may possibly shorten it. However, we don't know all the possible effects of the infusion because it is research.

Here is a copy of the consent form for you to assent to, so why don't you look at it and see whether you want to participate. You don't have to do it at all. It won't affect your care from me whatever you decide.

[Janey takes the papers and begins to read.]

Mrs. Granger: [points to the papers she has been reading] It says here that you stand to make a lot of money if this works and that none of the subjects will get any part of it. Is that fair? [Somewhat irritated].

Dr. Smith: Well that's the way it has been done. We don't want people to join research programs and take risks because they think that they might win some kind of lottery. Besides, don't you think that the people who thought of the idea and developed it should get the benefits.

Mrs. Granger: [annoyed but somewhat mollified] Well, not all the benefits. Since I trust you and am grateful to you I will sign.

Janey: It doesn't look like this stuff will hurt me and maybe it will get me out of here a little sooner. That sounds fair [giggles] and it's better if Mom is reluctant. I'll sign because I love you Doc and you're never on my case. She signs the forms.

Dr. Smith: Thanks. [Gives Janey a hug]

Case: Appropriateness of placebo controls

Matrix Pharmaceuticals developed a new drug that increased bone density in mice by facilitating osteoblast function without stimulating osteoclasts nearly as much, thus increasing bone density. Phase I and II trials were conducted with no significant morbidity at an effective dose.

A number of international experts in the field were asked to consult on the design of the hopefully definitive Phase III clinical trial that was going to be carried out at 100 sites in 15 countries.

Matrix's vice president for research proposed a placebo-controlled trial of 8,000 women over one year, with a direct measure of bone density, DEXA scanning, as the principal end point.

A European investigator indicated that they follow the latest version of the Helsinki Accord that indicated that placebo controls should not be used if there are effective standard therapies. In the case of osteoporosis, bisphosphonate were effective and relatively safe standard therapies.

An American representative pointed out that the FDA prefers placebo-controlled trials if there is no serious safety issue. Furthermore, he pointed out, comparison with an effective agent to demonstrate "non inferiority" or "superiority" would require a study of 30,000 women rather than 8,000, would take much longer, by vastly more expensive, and would require a greater number of adverse endpoints in both treatment categories to reach a conclusion, thus making it less safe over all for the research participants.

Company representatives agreed whole heartedly and suggested that the study be designed so that it focused on early findings, diminished bone density by DEXA and appropriate chemistries. The key to

a successful outcome and limited fracture morbidity would lie in the selection criteria for participants.

Another team member argued that an intermediate end-point like change in bone density by DEXA scan will not answer the question about preventing fractures. Bisphosphonates have been shown to reduce fractures already so that a new agent will have to be equal to or superior to them in protecting against fractures. In that case they will have to recruit women at high risk for osteoporotic fractures, for whom a placebo control is not benign at all.

Another team member added that with the availability of bisphosphonates, very few women with osteoporosis will be found in developed countries that are not taking an effective agent. Therefore most of the study will have to be done in developing countries.

There are plenty of untreated Americans if you look to underserved populations, stated one of the team.

Questions: Put yourself in the position of an ethics consultant to this meeting. What would you recommend as the most appropriate ethical randomized clinical trial for this new agent and give your reasons for the choice?

Case: Asthma Comparison

Asthma is a serious chronic problem in pediatrics. New drugs being developed for asthma need to be tested in children.

This study (an actual study) compared Beclomethasone (established therapy) with a new steroid that we will call NUSTER and placebo. Subjects were recruited from ages 12-16 and were required to have had asthma for at least 6 months and to have used steroids in the last 30 days, signifying serious shortness of breath.

The subjects were randomized to 4 groups and treated for 12 weeks: Beclomethasone bid, NUSTER 100 µg bid, NUSTER 200 µg bid, and placebo. Subjects would use albuterol, another standard agent, as needed. The main outcome measure was FEV₁, a measure of ability to take deep breaths. The study showed that all of the steroid doses were statistically equal and better than placebo, where FEV₁ deteriorated. Ten percent of the active treatment subjects and 44% of the placebo subjects had to discontinue the study because of shortness of breath.

The study was done in doctors' offices using a commercial IRB.

This study was published and used to support the introduction of NUSTER.

- 1. Was this an ethical study?**
- 2. Was a placebo control justified**
 - a. If the subjects were children?**
 - b. If the subjects were adults?**
- 3. Seven ethical requirements for clinical research as delineated by Emanuel et al are:**
 - a. scientific value**
 - b. scientific validity**
 - c. fair subject selection**
 - d. favorable risk/benefit ratio**
 - e. independent review**
 - f. informed consent**
 - g. respect for enrolled subjects**

Discuss this study with respect to each of these.

Nathan, RA et al; Ann Allergy Asthma Immunol 2001; 86: 203-10

Miller, FG, Storr AF; Chest 2002; 121:1337-42

Case: Alzheimer's Disease

Your basic research laboratory discovered the principal pathway by which β -amyloid was cleared from brain cells and was able to design an oligopeptide drug as a potential highly potent therapeutic agent to rapidly enhance clearing and support improvement of brain function.

With venture capitalists you formed a new company COGNI+ to license your discovery and complete development of this and potentially even more potent products. COGNI+ has conducted extensive investigations in an animal model of Alzheimer's disease and demonstrated that the agent appeared to produce few side effects and that intensive application for a week or two cleared the affected tissue of β -amyloid and that low dose maintenance could greatly improve the animals' condition.

COGNI+ filed an IND at the FDA to test humans. Based on the animal data, the most effective clinical trial for efficacy would be to treat patients with moderately severe Alzheimer's disease rather than early or advanced cases.

Your academic clinical responsibilities include supervision of a large nursing home where 35% of the patients have Alzheimer's disease. Therefore, you arrange to do the Phase 1 and Phase 2 trials in this facility. You review all the charts of patients to find the ones with moderately severe Alzheimer's disease.

The Phase 1 trial will test toxicity in 6 subjects. If the toxicity is low, it will be possible to proceed to the Phase 2 trial.

The Phase 2 trial will include 10 subjects in an escalating dose protocol to test efficacy. Because the drug clears rapidly it must be given intramuscularly three times a day in the acute phase of therapy.

Questions:

- 1. Would the IRB and the University-Industry Conflict of Interest Committee of your institution have a problem with this study?**
- 2. How will you determine whether participants can consent for themselves? What should you do if some cannot?**
- 3. How will you present the studies to the subjects and to their surrogates?**
- 4. This category of patients experiences a lot of “sundowning.” Will this likely affect your study?**

Expecting the Phase I and II trials to be highly successful from the basic mechanism and the animal experiments, you are planning a phase 3 clinical trial that will involve 300-400 participants.

- 5. What ethical issues must you consider in this large trial?**

Chapter 3: Bibliography

Experimental Design

Adrian, S. (2005). "Placebo effects in developmental disabilities: Implications for research and practice." Mental Retardation and Developmental Disabilities Research Reviews **11**(2): 164-170.

The author discusses the importance of a placebo in the trial of secretin injections in autism research. She then elaborates on the "Hawthorne effect" and elaborates on the physiological consequences of placebos. A very worthwhile read.

Carpenter, W. T., Jr., P. S. Appelbaum, et al. (2003). "The Declaration of Helsinki and Clinical Trials: A Focus on Placebo-Controlled Trials in Schizophrenia." Am J Psychiatry **160**(2): 356-362.

This provides an excellent analysis of the placebo-control problem generated by the 2000 version of the Declaration of Helsinki as modified in 2001 and formally appeared in October 2002. It argues for the proper use of placebos and the benefits of having them in studies where numbers are important, failure to respond to current meds is widespread and in cases where the availability of standard Rx is problematic.

Tishler, C. L. and S. Bartholomae (2003). "Repeat participation among normal healthy research volunteers: professional guinea pigs in clinical trials?" Perspectives in Biology and Medicine **46**(4): 508-20.

The authors try to determine the amount of repeat volunteerism, motivation (altruism, money, obligation), ethical, and methodological problems and some suggestions.

Richardson, L. (2005). "The ethics of research without consent in emergency situations." Mt Sinai J Med **72**(4): 242-9.

This is an excellent review of the federal rule that permits research without consent in emergency situations. The detail about the limitations and the arguments about whether personal therapeutic benefit must be part of the process are discussed.

<http://www.mssm.edu/msjournal/72/724242.shtml>

Whitehead, J. (2004). "STOPPING CLINICAL TRIALS BY DESIGN." Nature Reviews Drug Discovery 3(11): 973.

This paper discusses the DSMB stopping rules which, he says, should be built into the design, before efficacy, lack of safety, or inevitably no evidence of benefit. If you belong to a DSMB or have one on your study this is very worthwhile reading.

http://www.nature.com/nrd/journal/v3/n11/abs/nrd1553_fs.html

Weijer, C. and P. B. Miller (2004). "When are research risks reasonable in relation to anticipated benefits?" Nat Med 10(6): 570.

The authors propose to use "component analysis" to assess risk vs. benefit in clinical research. The therapeutic components are assessed differently from the non-therapeutic. They use equipoise to justify the therapeutic component.

<http://www.nature.com/nm/journal/v10/n6/abs/nm0604-570.html;jsessionid=00E29673439DE2E30C826750460B6D20>

Morris, M. C., V. M. Nadkarni, et al. (2004). "Exception From Informed Consent for Pediatric Resuscitation Research: Community Consultation for a Trial of Brain Cooling After In-Hospital Cardiac Arrest." Pediatrics 114(3): 776-781.

Hypothermia may help treat cardiac arrest in children, but it must be applied quickly. A research project studying their potential benefit without prior consent was proposed to the community and substantial support was obtained but the results were far from unanimous. This study requires Federal approval as well. They concluded that making sure that prospective cardiac arrest parents be notified and allowed to decide whether to participate in advance but that timely consent was not feasible.

<http://pediatrics.aappublications.org/cgi/content/full/114/3/776>

Roberts, L. W., T. D. Warner, et al. (2004). "Schizophrenia research participants' responses to protocol safeguards: recruitment, consent, and debriefing." Schizophrenia Research 67(2-3): 283.

This report describes interview of patients with schizophrenia who were currently involved in a research program. They indicate that the participants understood that they were involved in research and that they had agreed voluntarily to participate although some degree of coercion was noted. This is a worthwhile report for anyone considering research with vulnerable populations.

<http://www.sciencedirect.com/science/article/B6TC2-48Y0DV3-3/2/eaafedba809650b94c8231b368ecded>

Markman, M. (2004). "Ethical Conflict in Providing Informed Consent for Clinical Trials: A Problematic Example from the Gynecologic Cancer Research Community." Oncologist 9(1): 3-7.

This thoughtful article raises a series of ethical dilemmas regarding a study of "consolidation" therapy for women who achieve a complete clinical remission of ovarian carcinoma. They use the actual conduct of the experiment as the basis for discussion and also introduce the special responsibilities of the initial major study to be as complete as possible.

<http://theoncologist.alphamedpress.org/cgi/content/full/9/1/3>

Ross, L. F. (2003). "Responding to the Challenge of the Children's Health Act: An Introduction to Children in Research." Theoretical Medicine and Bioethics 24(2): 101.

This article summarizes the arguments in this issue of theoretical medicine regarding the challenge of the Children's Health Act of 2001 that provided both funding and the opportunity to loosen restrictions on research with children. It clearly summarizes sophisticated arguments and could introduce the field to a novice.

<http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/A:1024650410202>

Rothmier, J. D., M. V. Lasley, et al. (2003). "Factors Influencing Parental Consent in Pediatric Clinical Research." Pediatrics 111(5): 1037-1041.

In research with small children one might ask why are parents consenting. This study queries 44 parents or guardians regarding volunteering their children and found that the leading reason was neither altruism nor free medications, but rather to learn more about the disease. Nicely done.

<http://pediatrics.aappublications.org/cgi/content/full/111/5/1037>

Katzman, D. K. (2003). "Guidelines for adolescent health research." Journal of Adolescent Health **33**(5): 410.

This is an excellent description of the need for research on adolescents, their ability to consent, and the federal rules as interpreted for adolescents.

<http://www.sciencedirect.com/science/article/B6T80-49W1YBN-G/2/a66b9af2a5f68c67a6695a167276dbcd>

Macklin, R. (2000). "Informed consent for research: international perspectives." J Am Med Womens Assoc **55**(5): 290-3.

A brief and thoughtful analysis of two conditions under which women are treated unethically in becoming research participants, not being fully informed and having a husband also sign the consent form. She doesn't buy into either condition.

Hougham, G., G. Sachs, et al. (2003). "Empirical research on informed consent with the cognitively impaired." IRB Ethics and Human Research **25**(5): S26-S32.

This paper briefly describes research on informed in a great variety of cognitively impaired subjects at a number of institutions. While the data are not given conclusions derived from these studies are presented. Many cognitively-impaired individuals retain the capacity to make informed participation decisions. Consent is a longitudinal process with involvement of surrogates at every point. One should never ignore the wishes of impaired subjects. This paper provides useful insights and a number of the papers should be out by now.

Spriggs, M. (2004). "Canaries in the mines: children, risk, non-therapeutic research, and justice." J Med Ethics **30**(2): 176-181.

This report discusses the Kennedy-Krieger lead point study and why it was unethical, using insights different from matters of risk. Very worthwhile in considering what is good science.

Iltis, A. S. (2005). "Stopping trials early for commercial reasons: the risk-benefit relationship as a moral compass." J Med Ethics **31**(7): 410-414.

Drug trials are very carefully designed. They are approved because they have a favorable risk to benefit ratio. The authors argue that when companies stop trials for commercial reasons rather than matters of safety or efficiency they change the risk to benefit analysis unfavorable and, in doing, violate research ethics. This is an interesting and useful article.

<http://jme.bmjournals.com/cgi/content/full/31/7/410>

Tishler, C. L. and S. Bartholomae (2002). "The recruitment of normal healthy volunteers: a review of the literature on the use of financial incentives." J Clin Pharmacol **42**(4): 365-375.

The authors review studies that currently exist regarding the impact of financial incentives to healthy volunteers and discuss the "coercive" impacts of large payments. It sounds a lot like paternalism to me in that the arguments assume that people would violate their interests should they volunteer primarily for money. Who is to say what is in someone's best interests but the person?

<http://jcp.sagepub.com/cgi/content/abstract/42/4/365>

Grady, C. (2005). "Payment of clinical research subjects." J. Clin. Invest. **115**(7): 1681-1687.

The author analyzes the details of payment for participation in clinical research, mainly in support of appropriate payments.

<http://www.jci.org/cgi/content/abstract/115/7/1681>

Bennett, C. L., J. R. Nebeker, et al. (2005). "The Research on Adverse Drug Events and Reports (RADAR) Project." JAMA **293**(17): 2131-2140.

This report highlights the productivity of the RADAR (Research on Adverse Drug Events and Reports). The team identified and tried to quantitate 16 adverse reaction to approved drugs that were previously unknown. This study highlights the weaknesses of the adverse event reporting system (or non-system), It lends support toward enhancing the FDA's capacity to utilize the AE reporting system and the huge advantages inherent in developing a national database using electronic medical records.

<http://jama.ama-assn.org/cgi/content/full/293/17/2131>

Miller, F. G. and H. Brody (2003). "A critique of clinical equipoise. Therapeutic misconception in the ethics of clinical trials." Hasting Center Report **33**(3): 19-28.

This sophisticated article argues that research differs from clinical medicine and that the concept of equipoise contains within it a "therapeutic misconception." Very worthwhile arguments are made in the context of an excellent review.

Steinbrook, R. (2005). "Gag Clauses in Clinical-Trial Agreements." N Engl J Med **352**(21): 2160-2162.

This report discusses the evils of contracts with clinical research sponsors in which the investigator doesn't see all of the data before agreeing to publication.

<http://content.nejm.org/cgi/content/extract/352/21/2160>

Friedrich, M. J. (2005). "Neuroscience Becomes Image Conscious as Brain Scans Raise Ethical Issues." JAMA **294**(7): 781-783.

<http://jama.ama-assn.org/cgi/content/full/294/7/781>

This brief perspective points to ethical dilemmas generated by FMRI in practice but especially in research. Findings can be interpreted to violate privacy by revealing emotions that one would normally hide. Furthermore, the very act of doing FMRI would reveal unexpected findings of variable clinical significance in 2-8% of scans. How to deal with these raises additional ethical dilemmas the handling of which is very variable.

Franck, L. (2005). "Research with newborn participants: doing the right research and doing it right." J Perinatal and Neonatal Nursing **19**(2): 177-86.

This paper discusses the role of the neonatal nursing team in determining what research is ethical in the NICU and how the rights of the infants need to be protected.

Miller, F. G. and D. Wendler (2004). "Assessing the ethics of ethics research: a case study." IRB Ethics and Human Research **26**(1): 9-12.

These authors analyze research into clinical research ethics that employs deception. The argument is made that deception causes harm and thus risk vs. benefit arguments are relevant. They also deal with an informed consent that is a lie.

Weijer, C. (2003). "The ethics of placebo-controlled trials." J Bone Miner Res **18**(6): 1150-3.

This bioethicist challenges the concepts of Ellenberg and Temple regarding placebo controlled trials by elaborating on the concepts of risk. He argues that there are no good definitions or assessments of risk and that the case for a "sensitivity problem" is weak. He has no solution. Worth reading.

Rosenblatt, M. (2003). "Is it ethical to conduct placebo-controlled clinical trials in the development of new agents for Osteoporosis? An industry perspective." J Bone Miner Res **18**(6): 1142-5.

This industry wide discussion of the appropriate research design for drug trials in osteoporosis is very specific and responsive to concerns about the use of placebos. They suggest low-risk subjects, bone densities rather than fracture end points, extrapolation to and study of high risk subjects in a second trial, a reduced duration of study and an indication for prevention first. This interesting industrial response is well thought out and persuasive.

Ellenberg, S. (2003). "Scientific and ethical issues in the use of placebo and active controls in clinical trials." J Bone Miner Res **18**(6): 1121-4.

This discussion by a member of the FDA office of biostatistics and epidemiology confronts the difficulties of equivalence or non-inferiority studies in comparison to placebo-controlled randomized clinical trials. Although not an official document, it provides the FDA rationale for greatly preferring placebo controls. A very good paper.

Heaney, R. (2003). "Ethical issues in the design of osteoporosis clinical trials: the state of the question." J Bone Miner Res **18**(6): 1117-20.

This discussion of study design in osteoporosis work, clearly and thoroughly discusses the issues regarding randomized control trials, placebo controls, and surrogate markers by an expert in osteoporosis research. Very worthwhile.

Cummings, S., K. Giacomini, et al. (2002). A Strategic Plan for Clinical Research at UCSF: 2-7 .

The authors propose that UCSF develop an integrated, interdisciplinary and interschool Clinical Research Program. They think it needs a home of 150-200,000 square feet where those involved in the field could be housed, near each other and their subjects. They also suggest the creation of hubs for clinical research to provide the infrastructure. All of this would be connected via an electronic network for research. They also propose funding start-up clinical research through internal grants. This is a very far-seeing and expensive proposal, but if you don't think big, you will never accomplish anything big.

DeAngelis, C., J. M. Drazen, et al. (2004). "Clinical trial registration: a statement from the International Committee of Medical Journal Editors." *CMAJ* 171(6): 606-607.

This development, which is incomplete and applies only to a limited but extremely important group of journals simply states that clinical trial registration must take place before initiation of subject registration to be considered for publication. The registers must be transparent, independent and include the key information about the trial.

Marshall, E. (2004). "ANTIDEPRESSANTS AND CHILDREN: Buried Data Can Be Hazardous to a Company's Health." *Science* 304(5677): 1576-1577. This news article summarizes the Paxil in adolescents controversy. It raises questions about the right of drug companies to sequester data that they own and paid for, in the face of society's need to know. This question has littered the courts with respect to asbestos, silica, tobacco, cell phone radiation, etc.

Abboud, L. (2004). Drug Makers Seek to Bar "Placebo Responders" From Trials. *The Wall Street Journal*: B1, B5. June 18, 2004.

An interesting article that brings to light controversial topic in clinical trial design. Should pharmaceutical companies be allowed to manipulate subjects participating in their study?

Agrawal, M. and E. J. Emanuel (2003). "Ethics of Phase 1 Oncology Studies: Reexamining the Arguments and Data." *JAMA* 290(8): 1075-1082.

This is an important review of the literature evaluating Phase 1 clinical oncology trials to see whether the claims that the risk-benefit ratio is poor, the degree of understanding of the procedures is deficient and that coercion is routine are correct. They show that on balance, patients do a little bit better than expected, so benefits occur, that they understand what they are getting in to and finally that people with advanced cancer are willing to take risks for a possibility of improvement or cure. The lessons are to avoid underestimating the research participant. They may not know everything but they have a pretty good idea of what's important to them.

Antman, K., S. Lagakos, et al. (2001). "Designing and Funding Clinical Trials of Novel Therapies." *N Engl J Med* 344(10): 762-763.

This well-written article discusses the difficulties and importance of funding large-scale studies. Because larger trials have a greater chance of proving statistical significance, lack of subjects is a hindrance to study design. They suggest using a small percentage of health insurance premiums to fund the NIH and increase the scope of all studies.

Bailar, J. C., III (2001). "The Powerful Placebo and the Wizard of Oz." *N Engl J Med* 344(21): 1630-1632.

The placebo is an unchallenged staple of study design necessary to determine efficacy. While it contrasts a treated group of subjects, it does not distinguish between the natural course of disease and the "placebo effect." This article shows that a placebo has no benefit over nontreatment and may actually harm the doctor-patient by exposing patients to deception.

Benson, K. and A. J. Hartz (2000). "A Comparison of Observational Studies and Randomized, Controlled Trials." *N Engl J Med* 342(25): 1878-1886.

In our enthusiasm for randomized clinical trials, we tend to relegate observational studies to a lower level of scientific validity, especially because it is believed that the effects are generally larger in the observational studies. These investigators did a combined meta-analysis of observational clinical trials comparing two agents for the treatment of a condition and found randomized trials that compared the same treatments for the same conditions. They found 136 reports on 19 conditions that fulfilled the requirements. In only 2 of the 19 studies did the results of one method lie outside of the 95% confidence limits of the other. They conclude that there is no evidence in studies since 1985 for a systematic difference in outcome between the two modes of study.

Brody, J. (2002). Ferreting for Facts in the Realm of Clinical Trials. *The New York Times*. October 15, 2002.

A short article stressing participation in clinical trials for novel treatments. Useful for beginning readers but offers no analysis of study design.

Concato, J. S., N; Horowitz, R. (2000). "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs." *N Engl J Med* 342(25): 1887-92.

This paper challenges the assumption that observational (case-control) studies overestimate efficacy of treatment. By analyzing corresponding confidence intervals of five topics, it raises questions about trial design and the need for randomized, controlled trials.

Davis, M. M. and J. D. Lantos (2000). "Ethical Considerations in the Public Policy Laboratory." *JAMA* 284(1): 85-87.

Vulnerable populations necessitate the most amount of protection from negative interests and influences. The paper examines how negative incentives are used to encourage immunization in children and the ethics behind public policy trial design. Do they need as much stringency as clinical trials?

Dickert, N. and C. Grady (1999). "What's the Price of a Research Subject? Approaches to Payment for Research Participation." *N Engl J Med* 341(3): 198-203.
<http://content.nejm.org/cgi/content/full/341/3/198>

The article discusses the ethics of paid research subjects in terms of three models of payment: market, wage-payment, and reimbursement. Though all have their advantages, the authors conclude the wage-payment model is superior. Although it may be the most ethical, it does not seem as effective in recruiting research subjects. Some interesting analyses of the differences are provided.

Enserink, M. (2000). "BIOETHICS: Helsinki's New Clinical Rules: Fewer Placebos, More Disclosure." *Science* 290(5491): 418-419.

The article breaks the approval of the Declaration of Helsinki and shows its contradictions to current FDA guidelines. An interesting summary with a basic, but well thought out argument.

Federman, D. D. (2003). "Minimizing Risk in Clinical Research." *Ann Int Med* 139(1): 71-72.

This important editorial identifies the three pillars of protecting individuals from harm in randomized, controlled trials: the evolution of published ethics papers, most notably the Belmont Report, the IRB, and the informed consent process. It points out that each process is fallible and constantly evolving, giving way to litigation against lapses in protection and a constantly improving system.

Freedman, B., Ph.D. (1987). "Equipose and the ethics of clinical research." *N Engl J Med* 317(3): 141-145.

Freedman proposes that justification of clinical research either requires genuine uncertainty on the part of the principal investigator as to the efficacy or safety of the various trial arms, or (his new idea) that uncertainty of professionals as a whole as to the advantages of one or another arm justifies research even if the PI is convinced of the advantage of one of the arms. He suggests that this will make more research meet ethical standards. As will be seen, continuing of discussion of equipose is taking place.

Gale, E. A. M. (2001). "Lessons from the glitazones: a story of drug development." *The Lancet* 357(9271): 1870.

This report deals with the troglitazone story, which is pretty interesting but somewhat old hat in the face of new problems with Cox 2 inhibitors and SSRIs.

Grant, G., O. Guyton, et al. (1999). "Creating effective research compliance programs in academic institutions." *Acad Med* 74(9): 951-71.

This somewhat outdated paper discusses the creation of a voluntary compliance program in research institutions to assure adherence to federal regulations. Because of differing rules among research institutions it would seem to be a good idea; however, it might significantly decrease trust in academic research and place a burden on the IRB process.

Hellman, S. and D. Hellman (1991). "Sounding Board: Of Mice But Not Men." *N Engl J Med* 324(22): 1585-9.

Hrobjartsson, A. and P. C. Gotzsche (2001). "Is the Placebo Powerless?- An Analysis of Clinical Trials Comparing Placebo with No Treatment." *N Engl J Med* 344(21): 1594-1602.

This empirical meta-analysis reviewed studies in which placebo was one arm of the trial. The placebos could be pills, manipulations, or conversations. They were able to study 114 such trials. They found that the placebo had little to no effect when the results were binary whether the outcome was subjective or objective. With continuous outcomes there were placebo effects but they diminished with increasing sample size. In the treatment of pain the placebo demonstrated a reduction in pain intensity of 6.5 mm on a 100-mm visual-analogue scale. This study generated a lot of comment on the trial use of placebos for lack of efficacy. There is also much thought deriding the use of placebos when effective therapies are present except under exceptional circumstances.

Kodish, E., M. Eder, et al. (2004). "Communication of Randomization in Childhood Leukemia Trials." *JAMA* 291(4): 470-475.

This empirical study of children with leukemia and their parents tried to determine the degree of understanding of the concept of randomization (to new treatment and standard treatment arms). Most children with persistent leukemia end up in clinical trials. They found that only 50% of parents had an understanding of the concept of randomization. Having a nurse present and more complete explanation of the details of the research increased the percentage of the parents who understood the concept. leukemia trials.

Lilford, R. J. (2003). "Ethics of clinical trials from a Bayesian and decision analytic perspective: whose equipoise is it anyway?" *BMJ* 326(7396): 980-981.

This important paper recognizes that preclinical and other data tend to increase the likelihood of a trial being successful and that standard statistics, especially in relation to determination whether there is equipoise between the treatment arms is inappropriate. Optimism is not necessarily inappropriate.

Marquis, D. (1999). "How to Resolve an Ethical Dilemma Concerning Randomized Clinical Trials." *N Engl J Med* 341(9): 691-693.

An inherent dilemma exists in physicians recommending standard treatment over an unproven clinical trial. Physicians do not want to be responsible for referring their patients to failed trials, therefore they negate enrollment when giving advice to patients. The paper offers a strong recommendation that emphasizes informed consent as the vehicle to overcome this dilemma.

Marshall, E. (1998). "Controversial Trial Offers Hopeful Result." *Science* 279: 1299.

This article sheds light on a very controversial study testing the efficacy of a new AZT regimen in reducing *in utero* AIDS transmission. Researchers gave half the subjects a placebo, significantly increasing the statistical power of their study; however, this knowingly doubled their risk of transmitting the virus. Should long-term prevention be sacrificed to ensure greater subject protection?

Miller, F. G. and H. Brody (2003). "A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials." *The Hastings Center Report* 33(3): 19-28.

A predominant ethical view holds that physician-investigators should conduct their research with therapeutic intent. And since a physician offering a therapy wouldn't prescribe second-rate treatments, the experimental intervention and the bet proven therapy should appear equally effective. "Clinical equipoise" is necessary, but this perspective is flawed. The ethics of research and of therapy are fundamentally different, and clinical equipoise should be abandoned.

Moynihan, R., L. Bero, et al. (2000). "Coverage by the News Media of the Benefits and Risks of Medications." *N Eng J Med* 342(22): 1645-1650.

This study of newspaper and TV stories covering three drugs, pravastatin, alendronate and aspirin demonstrated that the information was usually incomplete about the benefits, risks and especially the costs of the treatment. Of greater concern was that the interviewed and quoted "experts" without indicating their ties to the manufacturer of the drug. I must say, the results are not surprising as drug companies are major advertisers and were determined to spin their drugs to best advantage.

Nathan, D. and D. Weatherall (2002). "Academic freedom in clinical research." *N Engl J Med* 347(17): 1368-71.

The article examines the Olivieri debacle that stemmed from cessation of the deferoxamine trial. It brings up an interesting point about trial design and confidentiality: who has a right to terminate industry-academia trials, the manufacturer or the investigator?

Oldham, R. (2005). Unlucky Jim. *Wall Street Journal*. February 18, 2005.

This short but effective news article chronicles a patient who succumbs to cancer after failed attempts to receive novel therapies in kidney cancer. It points out the failures of clinical trial selection criteria to deliver medicine to those in most dire need.

Ramsay, D. W., S. (2001). "The Use and Usefulness of Placebo Controls." *Science* 294(5543): 785.

The "placebo effect" can mar research results and diminish drug effects in clinical trials. With our society becoming increasingly dependent on drugs, we are also becoming conditioned to feel a drug effect when it is not really there. Interesting article.

Saunders, C., A. Sugar, et al. (1999). "What's the Price of a Research Subject?" *N Engl J Med* 341(20): 1550-52.

<http://content.nejm.org/cgi/content/full/341/20/1550>

This collection of letters in response to Dickert and Grady's July 15 article gives a full range of opinions on the topic of paid research subjects. They are nice replies.

Rothman, K. J. and K. B. Michels (1994). "The Continuing Unethical Use of Placebo Controls." *N Engl J Med* 331(6): 394-398.

The authors argue that placebos violate the basic principle of protection, and that they are being overused in research studies. Although old, it provides ethical justification for the revised Declaration of Helsinki. The authors recommend holding study designers accountable for misuse of placebos as well as stricter enforcement of placebo use requirements. A worthwhile read and is a cornerstone of the minimizing placebo use argument.

Russo, E. (2002). "The Biological Basis of the Placebo Effect." *The Scientist*: 30-31.

This approachable article gives empirical evidence, including PET scans and trial results, which illustrate placebos' positive treatment effects. Though the article does not mention it, this evidence endangers the placebo's place as a controlled way to examine trial results.

Shapiro, H. T. and E. M. Meslin (2001). "Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries." *N Engl J Med* 345(2): 139-142.

From the National Bioethics Advisory Commission a discussion of what ethical standards should be used for research overseas with particular attention to developing countries. This article takes the position that standards cannot be relaxed and that control subjects should receive the best therapy available in the developed world even though it will likely not be available after the trial. The authors also deal with

key issues including informed consent, research review, and post trial benefits to participants and their community. They discuss the use of placebos as well.

Spiegel, D., H. Kraemer, et al. (2001). "Is the Placebo Powerless?" *N Engl J Med* 345(17): 1276-1279.

These are a series of responses to Hrobjartsson and Gotzsche's article examining their methods and critiquing their results. The letters provide wonderful additional analysis to the article and are well worth reading.

Steinbrook, R. (2003). "Trial Design and Patient Safety -- The Debate Continues." *N Engl J Med* 349(7): 629-630.

The article gives an account of OHRP's recommendations on two disputed clinical trials for treatment of acute respiratory distress syndrome (ARDS). The OHRP concluded that in both cases the IRBs released informed consent documents that were too vague.

Sung N., Crowley W J et al. (2003). "Central challenges facing the national clinical research enterprise." *JAMA* 289(10): 1278-87.

This is an excellent position paper identifying the weaknesses underlying clinical research in the US. These are inadequate public trust and participation, lack of effective computerized systems to manage the data and other inefficiencies resulting in high costs, an inadequately trained work force, physicians included, and inadequate funding from the usual sources. These inadequacies have resulted in blockage of the translation of basic research into clinical studies and the blockage of the translation of clinical research results into clinical practice. They would like to see these issues addressed and improvement in the apparatus for bringing improved therapy into the lives of patients.

Vieira, C. (2002). "Brazil. Tough placebo rules leave scientists out in the cold." *Science* 295(5553): 264.

<http://www.sciencemag.org/cgi/content/full/295/5553/264>

Brazil's ban of all placebos in cases where effective treatment was available has drawn criticism from the country's clinical researchers. Although the policy protects subjects, it also closes them to novel therapies and significantly slows the rate of research.

Warner, S. (2004). "The Tribulations of Clinical Trials: Efforts are afoot to improve the output of the drug research pipeline." *the Scientist* 18(8): 20-24.

An extremely informative brief review of the problems associated with bringing a drug from concept to approval. It includes looking at problem areas and suggests empirical processes. A considerable amount of factual information is presented succinctly.

Weijer, C. M., P. (2003). "Rehabilitating Equipoise." *Kennedy Inst Ethics Journal* 13(2): 93-118.

Winslow, R. (2005). What Makes a Drug Too Risky? There's No Easy Answer. *Wall Street Journal*: B1-B2. February 16, 2005

This is an intriguing news article that offers a society-based rather than empirical view of risk. With pulled medications like Vioxx and negative reports of SSRIs and other drugs dominating media, there is no easy answer on what constitutes a "safe" drug. The author argues because the risk is small, even if it is significant, the medications should be allowed because of their benefit.

Mastroianni, A. C. and J. P. Kahn (2002). "Risk and Responsibility: Ethics, *Grimes v Kennedy Krieger*, and Public Health Research Involving Children." *Am J Public Health* 92(7): 1073-1076.

This article describes the Kennedy Krieger Institute study of lead reductions in low income housing in Baltimore that led to suits for lead exposure to children living in that housing. The Appeals Court decision sent the case back to the trial court with much criticism but the final disposition does not seem to have been reached.

Lockwood, A. H. (2004). "Human Testing of Pesticides: Ethical and Scientific Considerations." *Am J Public Health* 94(11): 1908-1916.

The Environmental Protection Agency has not used the protections of the NIH and FDA in conducting trials to determine the risks associated with the use of individual pesticides. The author indicates that this cannot be ethically justified. Worthwhile reading. Changes are afoot.

Wendler, D., L. Belsky, et al. (2005). "Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit." *JAMA* 294(7): 826-832.

United States federal regulations allow institutional review boards (IRBs) to approve pediatric research that does not offer participants a "prospect of direct" benefit only when the risks are minimal or a "minor" increase over minimal. The federal regulations define minimal risks based on the risks "ordinarily encountered in daily life or during routine physical or psychological examinations or tests." In the absence of empirical data, IRB members may assume they are familiar with the risks of daily life and with the risks of routine examinations and tests and rely on their own intuitive judgment to make these assessments. Yet intuitive judgment of risk is subject to systematic errors, highlighting the need for empirical data to guide IRB review and approval of pediatric research. Current data reveal that car trips pose the highest risk of mortality ordinarily encountered by healthy children. On average, these risks are approximately 0.06 per million for children aged 14 years and younger, and approximately 0.4 per million for children aged 15 through 19 years. Riskier, but still ordinary, car trips pose an approximately 0.6 per million chance of death for children aged 14 years and younger and an approximately 4 per million chance of death for children aged 15 through 19 years. Participation in sports represents the upper end of the range of morbidity risks for healthy children. For every million instances of playing basketball, approximately 1900 individuals will sustain injuries, including 180 broken bones and 58 permanent disabilities. These findings suggest IRBs are implementing the federal minimal risk standard too cautiously in many cases. These data also raise the question of whether the federal minimal risk standard may sometimes fail to provide sufficient protection for children, prompting the need to consider alternative standards.

Miller, M. (2001). "Phase I cancer trials: a crucible of competing priorities." *Int Anesthesiol Clin* 39(3): 13-33.

This erudite yet clear exposition describes the intrinsic difficulty physicians have in divorcing their clinical responsibilities from the goals of research. Because of their role as healer, the physicians had difficulty conveying the idea that the trial was designed to demonstrate toxicity and no control of tumors is expected. This inability to confront the issue contributes greatly to the therapeutic misconception that is so widespread among the surveys.

Millat, B., F. Borie, et al. (2005). "Patient's Preference and Randomization: New Paradigm of Evidence-based Clinical Research." *World Journal of Surgery* 29(5): 596.

Studies of surgical procedures have rarely been randomized, markedly diminishing the validity of a trial through bias. The authors discuss that situation, review a number of professional randomization schemes, and propose one of their own. A number of these patients make an early choice whether they are willing to be randomized and the study is done on those who are. The others would be treated with their preference. To me, this does not seem to be so different from medical therapies. However, they also add another step in which a group of surgeons make an initial determination as to the need for the procedure. The study evaluates both randomized and non-randomized subjects according to patient or doctor preferences.

<http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s00268-005-7920-z>

Nagasako, E. M. and D. A. Kalauokalani (2005). "Ethical aspects of placebo groups in pain trials: Lessons from psychiatry." *Neurology* 65(12_suppl_4): S59-65.

These investigators ask how they may evaluate the appropriateness of the use of placebo arms in pain trials in the face of a wide range of effective therapies. They deal with what can be learned from prior work, quality of the proposed study, the likelihood of harm in the placebo arm, and the degree of harm and whether alternatives to the placebo are consistent with the research objectives and feasible.

http://www.neurology.org/cgi/content/abstract/65/12_suppl_4/S59

Kopelman, L. M. and T. F. Murphy (2004). "Ethical Concerns About Federal Approval of Risky Pediatric Studies." *Pediatrics* 113(6): 1783-1789.

This report explores the ethical considerations surrounding pediatric research grants in which children will be exposed to a greater degree of risk than any projected therapeutic benefit or in the performing experiments with greater than a minor degree of risk over "minimal" in healthy individuals. Such studies require the RIB to send the protocol to the department of HHS for approval by the secretary, the so-call "407 approval." This report analyzes the 407 process and finds it wanting or vague in a number of ways. A very good analysis.

<http://pediatrics.aappublications.org/cgi/content/full/113/6/1783>

Wendler, D. (2004). "Risk standards for pediatric research: Rethinking the Grimes ruling." Kennedy Inst Ethics Journal **14**(2): 187-98.

This think piece was directed at the Grimes (lead paint study in Baltimore) Ruling severely limiting research in children that provided no benefit but yet was associated with a certain amount of risk. This has stimulated much discussion of the risk limitations of pediatric research as well as attempts to assure that meaningful research care be carried out on pediatric patients.

Annett, R. D., J. L. Brody, et al. (2004). "Perception of risk associated with asthma research procedures among adolescents, parents, and pediatricians." Journal of Allergy and Clinical Immunology **114**(5): 1138.

This very nice paper addressed an important subject. By comparing risk levels as perceived by the adolescent subjects as well as parents and pediatricians, a strong perception of their views and a wide range of argument was found. In the perceptions of benefits, I think that they did not distinguish between clinical procedure and procedure for research purposes, especially spirometry. Parents and adolescents thought that placebo was beneficial, leading to concern over the subjects' perception of research.

<http://www.sciencedirect.com/science/article/B6WH4-4DR7WSG-W/2/f72ed7a1d125d3f53a77648ea2de794b>

Flynn, J. T. (2003). "Ethics of Placebo Use in Pediatric Clinical Trials: The Case of Antihypertensive Drug Studies." Hypertension **42**(5): 865-869.

This is a very useful paper in that it confronts the two issues of initial importance, when it's ok to use placebo and with which children it was reasonable to do that.

<http://hyper.ahajournals.org/cgi/content/full/42/5/865>

Onder, R. F. (2005). "The ethics of placebo-controlled trials: The case of asthma." Journal of Allergy and Clinical Immunology **115**(6): 1228.

The author, owner of a clinical research organization, supports the use of placebos in asthma trials for the usual reasons: ease of determining effectiveness, ability to measure adverse events better, evaluating somewhat less effective therapies, minimizing exposure to a trial of inefficacious agent, studying clinical situations in which withdrawal of a modality may be efficacious. Elaboration on the concept of assay sensitivity of a trial, the case is made that if standard therapy does not always produce statistical benefit then the trial is a weak method for showing superiority or non-inferiority, the requirement of a comparison study. A well done argument.

<http://www.sciencedirect.com/science/article/B6WH4-4FSCMDP-D/2/26f7dc0e9b2e74d424ee8a9c1d1394c0>

Wendler, D., L. Belsky, et al. (2005). "Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit." JAMA **294**(7): 826-832.

<http://jama.ama-assn.org/cgi/content/abstract/294/7/826>

This thoughtful paper tries to define risk in ordinary life for children in order to quantify the federal rule that children who participate in studies with no benefit to them not be exposed to risks greater than "ordinarily encountered in daily life or during routine physical or psychological examinations or tests." By using the risks of an auto accident or a sports injury one can perhaps define the risks to children to compare with the potential adverse effects of participating in research.

Onder, R. F. (2005). "The ethics of placebo-controlled trials: The case of asthma." Journal of Allergy and Clinical Immunology **115**(6): 1228.

<http://www.jacionline.org/article/PIIS0091674905003192/abstract>

Using asthma as the example, he indicates the rationale for conducting placebo-controlled trials. The include the usual -- better science, smaller number of subjects at risk, less chance for adverse events, and truly knowing the rate of adverse events. Others include the use of less effective (maybe cheaper) therapies.

Young, S. (1998). "Risk in research--from the Nuremberg Code to the tri-council code: implications for clinical trials of psychotropic drugs." J Psychiatry Neurosci **23**(3): 149-55.

The author discusses research risk as delineated by the Nuremberg Code, the Declaration of Helsinki and various Canadian guidelines. He concludes that none of them really define risk well. He then discusses the implication for research on psychotropic drugs.

Tigges, B. (2003). "Parental consent and adolescent risk behavior research." J Nurs Scholarsh **35**(3): 283-9.

This report compares active and passive parental consent for school-based behavioral research and comes clearly down on the side of passive consent. It has to be consistent with federal regulations to avoid the possibility of legal consequences.

Kiskaddon, S. H. (2005). "Balancing Access to Participation in Research and Protection from Risks: Applying the Principle of Justice." J. Nutr. **135**(4): 929-932.

This paper discusses the apparent conflict between applying the justice principle with the protection of subjects in the IRB approval process. The suggestion is made that proper application of the principles of autonomy and beneficence will facilitate adherence to the justice principle.

<http://jn.nutrition.org/cgi/content/full/135/4/929>

Nelson, R. M. and L. F. Ross (2005). "In Defense of a Single Standard of Research Risk for all Children." The Journal of Pediatrics **147**(5): 565.

This editorial is devoted to the idea that it is possible to develop a single standard of research risk for children and propose that the NIH develop such a standard -- as they suggest.

<http://www.sciencedirect.com/science/article/B6WKR-4HJGM1S-K/2/2ae919b789b8571af0b5b352217a36b0>

Wendler, D. and E. J. Emanuel (2005). "What is a "Minor" Increase over Minimal Risk?" The Journal of Pediatrics **147**(5): 575.

In response to JAMA 2004; 291: 476-2 the authors try to develop ethical guidelines whereby IRBs may approve research on children that could be considered a "minor increase over minimal risk." very well worth reading. See editorial.

<http://www.sciencedirect.com/science/article/B6WKR-4HJGM1S-S/2/a07a87d7e4cc5383a47886354cfdba0b>

Wendler, D. and H. Forster (2004). "Why we need legal standards for pediatric research." The Journal of Pediatrics **144**(2): 150.

This commentary discusses the implications of the Grimes case for legal liability of investigators carrying out research on children. They consider implications of 50 states writing different laws in the vein of them recently enacted Maryland law and warn investigators that their legal protections are slim.

<http://www.sciencedirect.com/science/article/B6WKR-4BKDKPD-R/2/003af6fbbdec811277c88f21a245f739>

Ross, L. F. (2003). "Do healthy children deserve greater protection in medical research?" The Journal of Pediatrics **142**(2): 108.

This commentary points out that the term "minimal risk" as utilized in reviewing research in children fails to distinguish between healthy and sick children, suggesting that for some reviewers, sick children can be exposed to more risk because they have already been exposed to greater risk. The author raises further questions as to the risks children can ethically be subject to.

<http://www.sciencedirect.com/science/article/B6WKR-48166F1-8/2/d289d9d96eb89d1094062a3c7d466b34>

Kimmelman, J. (2004). "Valuing risk: the ethical review of clinical trial safety." Kennedy Inst Ethics Journal **14**(4): 369-93.

This very thoughtful theoretical paper considers risk assessments by IRBs and finds that they are too limited in that they are largely limited to technical evaluation of prior data. They usually are undetermined at the time of IRB consideration. At the same time, committees give less consideration to differing definition of risk of various populations and how they would attribute risk. This is very worthwhile, especially for IRB members.

Buchanan, D. and F. G. Miller (2005). "Principles of early stopping of randomized trials for efficacy: a critique of equipoise and an alternative nonexploitation ethical framework." Kennedy Inst Ethics Journal **15**(2): 161-78.

Early stopping of clinical trials for efficacy has become increasingly common. The usual reason given is that we can't expose subjects receiving the alternative treatment to inferior care since efficacy been proven, i.e. equipoise has been lost. The problem is that many such decisions leave the research incomplete. The author addresses the situation and proposes a new stricter standard that takes into greater account the generation of new knowledge. Required reading for NSMB members.