

Teaching the Responsible Conduct of Research in Humans (RCRH)

home

contact us

chapters

introduction ▶

chapter 1 ▶

chapter 2 ▶

chapter 3 ▶

chapter 4 ▶

chapter 5 ▶

chapter 6 ▶

chapter 7 ▶

chapter 8 ▶

Resources

links

the Responsible Conduct of Research In Humans (RCRH)

Stanley G. Korenman M.D.

Home: Table of Contents

- Introduction
 - Scenarios
 - Bibliography
- Chapter 1: The Ethical Basis of RCRH
 - The Nature of Science
 - Research Integrity
 - Professionalism in Science
 - Cases
 - Practical Elements of Responsible Research Conduct
 - Bibliography
- Chapter 2: Research in Humans
 - History of Rules About Research in Humans
 - Definitions
 - Federal Mandate
 - Respect for Persons
 - Beneficence
 - Justice
 - Common Rule
 - Institutional Review Board (IRB) Mission
 - Cases
 - Bibliography
- Chapter 3: Ethics and Study Design
 - Introductory
 - Ethics Design
 - Appropriate Risk to Benefit Ratio
 - Selection of Subject Populations
 - Cases
 - Bibliography
- Chapter 4: Conflicts of Interest (COI)
 - Definitions
 - Consequences of a COI

<http://www.medsch.ucla.edu/public/korenman/default.htm>

- Government Intervention
- Industry Sponsorship
- Professional Societies
- Clinical Practice Guidelines
- Other Initiatives
- COI in Financial Consulting
- Cases
- Bibliography

- Chapter 5: International Clinical Research
 - Underlying Conditions
 - Approval and Monitoring Issues
 - Study Population Issues
 - Structural Issues
 - Epidemiological and Social Science Research
 - Cases
 - Bibliography

- Chapter 6: Monitoring Research
 - Cases
 - Bibliography

- Chapter 7: Genetics and Stem Cell Research
 - Genetics
 - Human Embryonic Stem Cell Research
 - Bibliography

- Chapter 8: Malfeasance and Misconduct
 - Definitions
 - Process
 - Whistleblowing
 - Litigation, the New Approach to Research Management
 - The Importance of Trust
 - Cases
 - Bibliography

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Teaching

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home

contact us

Chapters

Introduction ▶

chapter 1 ▶

chapter 2 ▶

chapter 3 ▶

chapter 4 ▶

chapter 5 ▶

chapter 6 ▶

chapter 7 ▶

chapter 8 ▶

Resources

links

the Responsible Conduct of Research in Humans (RCRH)

Links

- "What makes clinical research ethical?"
<http://jama.ama-assn.org/cgi/content/full/283/20/2701>
- "Protecting Subjects, Preserving Trust, Promoting Progress 1: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research"
<http://www.aamc.org/members/coit/firstreport.pdf>
- "Protecting Subjects, Preserving Trust, Promoting 2: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research"
<http://www.aamc.org/members/coit/2002coireport.pdf>
- "Is Academic Medicine for Sale?"
<http://content.nejm.org/cgi/content/extract/342/20/1516>
- "Scope and impact of financial conflicts of interest in biomedical research: A Systematic Review"
<http://jama.ama-assn.org/cgi/content/full/289/4/454>
- "Relationships between academic institutions and industry in the life sciences - an industry survey"
<http://content.nejm.org/cgi/content/abstract/334/6/368>
- "Doctors without Borders: Why you can't trust medical journals anymore"
<http://www.washingtonmonthly.com/features/2004/0404.brownlee.html>
- "Physician industry relations Part 2: Organizational issues"
<http://www.annals.org/cgi/reprint/136/5/403.pdf>

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Teaching the Responsible Conduct of Research In Humans (RCRH)

Stanley G. Korenman, M.D.

INTRODUCTION:

Since we published, "Teaching the Responsible Conduct of Research utilizing a Case Study Approach" in 1994 (AAMC Publications), the scientific community has addressed research integrity issues with energy and, I believe, with considerable success. Trainees routinely receive instruction in responsible conduct of research (RCR) and their mentors have become much more sensitive to the issues, partly because of their prior education and surely because of heightened public interest, regulation and accountability. Institutions have developed and updated policies regarding data, patent and licensure, collaboration, sharing, conflict of interest and misconduct. Faculty committing malfeasance or misconduct are no longer sacrosanct and problems are less likely to be whitewashed. Institutional managers, in their fiduciary roles have made great efforts to prevent expensive and embarrassing misadventures from taking place, with substantial but incomplete success.

Research involving human beings remains particularly challenging to the scientific community. Studying people, their tissues and their data raises ethical complexities not seen with basic research, including responsibility for the safety and privacy of study participants. Investigators must also help participants learn before, during and after a study the rationale, procedures and results of the study. Both international and domestic research require sensitivity to the cultural background and preferences of participants. Unlike molecular, cellular or animal studies, human subjects require fairness in participation, respect for their autonomy and protection from harm.

While every scientist needs to become well versed in the ethical issues surrounding basic research, clinical investigators have the additional responsibility to fully appreciate the ethical dilemmas characteristic of clinical investigation. But clinicians who do human research rarely have the time or inclination to study and teach the responsible conduct of research with humans (RCRH). The development of national initiatives to facilitate translational medicine including the Clinical Translational Science Award (CTSA) makes it imperative for the scientific teams that assemble to be fully cognizant of the issues surrounding human research. This E-book is designed to help them.

In this book we employ problem-based learning to address ethical questions involving research in humans. Each chapter contains an introduction, a glossary of terms, problem scenarios for discussion and annotated bibliographical references to

help readers find the sources they need. Needless to say, the policies, guidelines and regulations involving research with humans continue to evolve. Our society regularly upgrades its demands for accountability as social mores steadily evolve. Therefore, the literature must be updated regularly and new scenarios developed with the evolution of important ethical issues. A section on writing scenarios is thus included.

Scenarios:

The use of scenarios is an excellent way of making instruction in RCRH interactive. A good case scenario will stimulate discussion among the students. Course participants become involved and find themselves expressing opinions as their ethical sensibilities are aroused by the case. Cases also tend to eliminate the intimidating barriers to discussion found in classrooms where faculty, staff and trainees at various levels learn together (a highly desirable situation). In courses with guest speakers, controversial cases can generate interactions between instructors that add more spice and understanding to the presentations. The scenarios can often be examined from multiple points of view and simple solutions are not required or even desirable. The teacher will often act as facilitator and allows the students to take the lead in analysis, making sure only that the appropriate topics are considered. This permits the fostering of ethical sensitivity and teaches acceptance of uncertainty in RCRH.

Students tend to keep their cases and refer to them when personally confronted with an analogous ethical dilemma. Scenarios also make good essay examination questions as the students have to wrestle with questions they raise.

The cases presented in this E-book represent major issues confronting clinical investigators. They are error-ridden by design.

Course instructors can use their imagination in creating cases on their own. Good examples reach the public domain with all-too-great frequency. Individual scenarios should not attempt to deal with all the issues in research ethics, but rather should tackle a theme. Providing a number of questions for the audience to consider generally works well. It is worth providing specific demographic information about the individuals in the scenarios including gender, title and research status because the latter two will affect judgments about behavior. It's easier and more specific for students to refer to Edith Jones rather than "the graduate student." Good scenarios avoid excessive introductions and technical detail that creates "solutions" based on technical changes rather than confronting the ethical dilemmas.

RCRH involves adherence to a myriad of Federal, State and local regulations, guidelines, and idiosyncrasies. Incorporating local conditions as features of scenarios can be very useful in the instruction process.

Many of the cases could have been placed after more than one chapter as they cover a range of issues. That's reality. I tried to have an important issue related to each chapter considered in the case. Each of these cases has been tried in my course and found to be sufficiently provocative to engender active discussion.

Bibliography:

Each chapter has an extensive bibliography focused on articles published between 2000 and February 2006. Most of the bibliographic material is annotated. The principles of the annotation process are to avoid replicating the title and giving the details in the abstract. Rather, the idea is to give an idea of the type of work, (e.g. empirical, think piece, regulatory), its significance and its quality. URLs are available for most of the articles so it is easy to go up and see the abstract for details. I have not been totally consistent in these evaluations. Those who are interested in a reference will find it relatively easy to download the abstract or the whole article for study. Materials relevant to research ethics can be found in many journals and in other written sources. Although we were reasonably thorough, significant articles can be found, especially in books that were not referred to.

I want to acknowledge the extremely valuable assistance of Andrey Finegersh, my hardworking and thoughtful student assistant. Nothing could have been achieved without his help.

Chapter 1: The ethical basis of RCRH

The recent course of history in the Western world has been in the direction of greater freedom and self-determination of individuals. A logical result of that has been the movement from paternalism to autonomy in medical care and by extension in medical research. Great impetus to that movement was provided by the atrocities carried out in the name of research by the Nazi German physicians, as described in the reports of the Nuremberg trials. That led directly to the first clear statement of the relationship of research subjects to the investigator and to the research being proposed. (). However, a statement of principle, as ethically powerful and persuasive as it was, did not result in uniformly unimpeachable research performance. As a result of considerable consternation over several specific programs of human research in the United States, a national commission was convened under the direction of Kenneth Ryan that issued a report, (The Belmont Report) outlining appropriate research behavior. The commission proposed government control through Institutional Review Boards at research institutions. The report was enacted by Congress to encompass human research carried out under the auspices of a number of Federal agencies, hence The Common Rule. Subsequently the World Health Organization produced the Declaration of Helsinki that supported similar international rules and systems and provided special consideration for the populations of developing countries. That code has been modified and strengthened a number of times.

A. Nature of Science

Science can be thought of as the system of reasoning and communication that has, from the beginning provided our species with increasing control over its environment. Science is derived from the practical knowledge of craftsmanship that has been transferred within and between generations from prehistory. In the last 400 years scientific knowledge has distinguished itself by being observation-driven, cumulative and always tentative. Even its most hallowed theories remain in thrall to the next set of experiments for confirmation or denial. In the past hundred years, the sophistication of experiment and analysis has grown astonishingly deep so that only relatively small numbers of experts really understand the bases for far-reaching explanations of nature including cosmology, quantum mechanics, molecular structure, cellular systems and evolution. We benefit by that sophistication in every electronic gadget we employ, in every recombinant molecule with which we are treated, in new structural materials for medicine and everyday life, in improved weather prediction capacity, and in more efficient and pleasant housing and environs. We know that science works because technology works. We know that evolution is true because of its great explanatory power in all biological fields.

The general public remains puzzled by the conditional reasoning and probabilistic thinking that underlie the power of science. Nevertheless, research studies have come underlie legislation, nutritional recommendations environmental assessments and understanding of disease. To the extent that studies are done scientifically and marketed honestly, they contribute greatly to the general lawfulness and openness to change that characterizes Western Society. Societal dependence on science conveys on scientists a great ethical responsibility to conduct research with integrity. Improving research integrity was the charge of a NAS commission and the following paraphrases parts of the report ().

A. Research Integrity

Research integrity may be defined as active adherence to the ethical principles and professional standards essential for the responsible practice of research.

By active adherence we mean adoption of the principles and practices as a personal credo, not simply accepting them as impositions by rulemakers.

By ethical principles we mean honesty, the golden rule, trustworthiness, and high regard for the scientific record.

NAS report definition: “For individuals research integrity is an aspect of moral character and experience. It involves above all a commitment to intellectual honesty and personal responsibility for ones actions and to a range of practices that characterize responsible research conduct.” These practices include:

- “1. Honesty and fairness in proposing, performing, and reporting research;
2. Accuracy and fairness in representing contributions to research proposals and reports;
3. Proficiency and fairness in peer review;
4. Collegiality in scientific interactions, communications and sharing of resources;
5. Disclosure of conflicts of interest;
6. Protection of human subjects in the conduct of research;
7. Humane care of animals in the conduct of research;
8. Adherence to the mutual responsibilities of mentors and trainees.”

While science encourages (no, requires) vigorous defense of one’s ideas and work, ultimately research integrity means examining the data with objectivity and being guided by the results rather than by preconceived notions.

We will return to the importance of preserving the integrity of the scientific record in the section on misconduct.

B. Professionalism in Science

Professionalism in science denotes a pattern of behavior identified with scientific integrity that, in turn provides certain privileges. Like other professionals, scientists are expected to behave with intellectual honesty and excellence in thinking and doing. In many respects they perform their professional activities as a monopoly, licensed by society similar to doctors, nurses, lawyers, hairdressers, accountants, and real estate brokers. Besides providing their expertise, professionals are supposed to behave collegially and teach the skills to others, and put society's needs first in their professional activity. In response, society gives them a great deal of autonomy in conducting their professional lives. With scientists, that means selection of one's own research problems and methods of procedure. They also are given the responsibilities to allocate funding, and review of their output in publications. Like other professions they are given responsibility for discipline in the event of poor performance or malfeasance. When self-regulation fails to sustain honesty and high quality, society imposes rules and laws to maintain its interests in professional quality.

Table: Elements of Professionalism

Intellectual honesty Excellence in thinking and doing Collegiality and openness Autonomy and responsibility Self-regulation

C. Practical Elements of Responsible Research Conduct

1) Conducting and reporting research

Role of the hypothesis
Critical nature of experimental design
The tentativeness of conclusions
Skepticism and humility tempered with conviction
Dealing with surprises - serendipity
Communicating with colleagues
Communicating with the community- media

2) Social responsibility of scientists

Is it appropriate to consider the broader consequences of the pursuit of a scientific question?

"I just make discoveries about nature, others use my discoveries for better or worse (nuclear energy, synthesis of viruses, very toxic compounds)."

“I must consider the predictable consequences of my research and decide in advance if I will create serious ethical problems as a result of its outcomes.”

“It matters not that others might discover what I avoid seeking because of its consequences. I do not have to contribute to the misfortune of humanity in my research.”

“The true consequences of a research effort are impossible to predict and it is the height of arrogance not to pursue a promising avenue of science just because of qualms about its misuse.”

“How do I design and interpret my work not to bias the conclusions?”

“Do scientists have the responsibility to make every effort to enter their work into the scientific record whether it is positive or negative?”

3) Collegiality, sharing

This aspect of professional behavior has always been a core value of science. There is an NIH policy on sharing reagents, databases and transgenic animals. Materials Transfer Agreements (MTAs) routinely monitor the transfer of resources between labs and between institutions. On the other hand, science is so competitive that sharing may reduce credit to the lab and diminish the scientific achievement associated with the effort of the trainees in the lab, two of the major signs of research success. How to balance the two mandates is a serious challenge.

Patent and licensure are highly desired by research institutions and accrue benefit to investigators as well. They may require secrecy in research and sometimes result in closed laboratories where the trainees cannot discuss their work. This is incompatible with collegiality and sharing.

A major element of scientific integrity is the proper assignment of credit for past work of others and current work within the research group. Scrupulous adherence to this practice will help greatly but not eliminate dissatisfaction. Is there a process to ensure understanding and appropriate assignment of authorship and credit?

4) Mentorship

What is the essence of mentorship? Is it taking on a fiduciary responsibility for the trainee and putting her needs first? That too is one of the practices of research integrity. Questions arise such as, Is it appropriate for a PI to refuse to mentor the trainees in the lab? Is one mentor enough for a trainee or are they better off looking at least for a professional mentor and a research mentor? What are the responsibilities of mentors toward trainees? What are

the characteristics of good mentors? What are the responsibilities of trainees toward mentors?

5) Reviewing and monitoring research

This includes reviewing grants and research reports and serving on Data and Safety Monitoring Boards, Research Ethics Committees (IRBs) and other research oversight committees.

In all of these functions the individual involved must:

- Provide an objective review**
- Maintain confidentiality**
- Avoid conflicts of interest by recusal when appropriate**
- Avoid taking advantage of inside information**
- Maintain integrity of the scientific record**

6) Conflicts of interest and commitment

- Who is the scientist working for?**
- Definition of a conflict of interest – it's the situation**
- Managing conflicts of interest**
 - Disclosure**
 - Limited financial involvement**
 - Transactional transparency**
 - Oversight – monitoring, auditing,**

7) Scientific Malfeasance and Misconduct

- Fabrication Falsification and Plagiarism – definitions and distinction from error**
- Impact on the research record**
- Risk of litigation**
- Whistleblowing**
- Mandated institutional responses**
- Bad research manners- interpersonal relations – exploitation of subordinates, exploitation of inside knowledge,**

CASES Chapter 1

Immunology Graduate Student, Dubious Data

Darlene Campion, a PhD candidate in immunology gave her regular presentation of research progress when her PI said that her data looked great and that she should put together an abstract for the spring meeting with herself as first author. After the session Darlene basked in the pleasure of her success. However, nagging doubts about the solidity of her data resurfaced after the next set of experiments. She wanted to do more experiments but the abstract deadline was now only two weeks

away and she knew that she would not be able to complete further experiments before the deadline. She went to her PI Gabriella Corral.

“Darlene, she was told, you need to go out on a limb a little to be recognized. After all, the system runs on getting credit for doing something first and the innovation can provide recognition for years. Let’s put in the abstract and you can keep doing experiments until the meeting. In fact, by then you might have the paper written and submitted. This is a very competitive world, so compete girl, compete!”

Darlene, still dubious, sends in the abstract and redoubles her efforts to provide a solid base of experimental evidence to support the novel hypothesis. Meanwhile Dr. Corral heard from the Immunology society that the abstract was selected for a plenary presentation as one of the most significant developments of the year. Elated, she relates the honor to Darlene. Rather than the expected elation, Darlene turns very pale.

“As I said before, she states, the data don’t seem to be so great to me and I have not been able to substantiate the results.”

“Well, you still have a little time but if you get no further, we will just present the original material in the abstract,” says Dr. Corral.

Darlene hurriedly left the room.

Questions:

1. Is there any questionable behavior here?
2. Elaborate on the underlying theme in research ethics?
3. What are the options for each of the players if the data remain the same?

Case: Transhumans

It’s a short time in the future, say 2020. You have been studying brain processing in hopes of enhancing the cognitive capacities of patients with Alzheimer’s disease and those who are mentally retarded. You have just discovered a way of increasing the brain’s memory capacity by 100% and it’s processing speed two fold using the daily administration of 2 pills. You are overjoyed except for the fact that you know what happened when lesser improvements in cognitive function were introduced early in the 21st century. People started taking them to improve memory even though there was no evidence that they worked in normal persons. It was a reminder of what happened with steroids and growth hormone on physical performance in the 20th century. They became essential for every truly competitive athlete.

Your finding is so central to thought that those taking the drug will thoroughly outstrip everyone else that we might consider them to be transhuman. As you think about your discovery, you can visualize a situation in which the transhumans begin to take over the resources of the earth, and ultimately have no use for the “plain humans” they supplanted.

Questions:

- 1) What do you think as a scientist of this potential state of affairs?
- 2) Do you have any responsibility as a scientist to consider the consequences of your work when you think of what to do with your findings?
- 3) Science as a discipline deals with major technological developments including:
 - a. Nuclear power and bombs
 - b. Recombinant DNA technology

- c. Totipotent embryonic stem cells
- d. Reproductive technologies using genetic manipulation
- e. The Internet

Is it appropriate to allow the political process to determine who will make the critical decisions about the use of scientific advances?

Case: The Real Thing

Eckhard and Wimmer demonstrated the complete synthesis from oligonucleotides of the cDNA of poliovirus, from which infectious virus could be produced. They published these results in *Science*. Cello et al demonstrated that the production of the active virus could be carried out from scratch – one could say that a form of life was created. This received a lot of press play.

There was considerable criticism of both the authors and *Science* for publishing material that might be of use to terrorists. A number of congresspersons filed a resolution criticizing the publication. Although, in this case the virus is tiny and available, the method expensive and unwieldy, and the infectiousness quite limited, there is no doubt that by appropriate genetic manipulation, with enough money, agents like smallpox and anthrax could be produced by scientists and their results published.

Scientists have social as well as individual responsibilities.

Questions: 1. How can we handle the inevitably increasing capacity to create dangerous life forms?

As individual scientists?

As a society?

As an international scientific community?

Case: Sloppy Lab work

Background: During the first year of graduate school, Tom has been taking courses and doing laboratory rotations. While in Professor Allen's laboratory, Tom makes several exciting observations. Professor Allen tells Tom that the results will be publishable in a major journal.

Part 1: When Professor Allen goes to write the manuscript a month later, she finds that Tom did not record in his notebook the incubation medium and times for one group of experiments. Also, the computer files where Tom thinks he saved the information were accidentally erased.

Questions:

1. Can Professor Allen still write the paper?
2. Would it make a difference if Tom said he could remember the details even though he didn't write them down?
3. Would it make a difference if a technician working on the project said that he remembered even though Tom could not?

Part 2: Professor Allen writes the paper, which is accepted for publication. Tom finishes his first year and returns to Professor Allen's laboratory. He begins where he left off, but in two attempts he cannot repeat the original finding.

Questions:

1. What should he and Professor Allen do about the paper assuming it has not yet been published?
2. What should they do if the paper has been published?

Part 3: Professor Allen receives a manuscript to review that contains experiments whose results make clear why Tom has been unable to make further progress with his experiments.

Questions:

1. Can Professor Alan share this information with Tom?
2. What if the information was contained in a grant proposal?

Derived from Fred Grinnel

Case: Research Integrity

Jones is a highly successful entrepreneurial academic scientist. He occupies an endowed chair that allows him to avoid teaching. His research team performs brilliantly conceived studies with precision and completeness. His lab has made many important contributions and he is consistently very well funded.

A graduate student is considering Jones' lab for his Ph.D. and speaks to the current trainees. They say that Jones is merciless, requiring 15-hour days for months before the annual meeting abstract due date. He assigns projects without regard to the trainee's interests, has trainees compete with each other, unilaterally determines authorship and first authorship in what appears to be an arbitrary manner and deals with staff and trainees in a paternalistic and demeaning manner. He personally spends little time with his trainees and shows little interest in their lives. His usual comment is that research is extremely competitive and they had better learn how to fend for themselves. His trainees almost invariably get excellent positions after completing their degrees with him.

QUESTIONS:

1. Does the investigator have research integrity? Intellectual honesty? Defend your answer.
2. If you were the student, would you select his lab? Defend your answer.

3. The department chair and dean know all about this lab chief's behavior and have never discussed it with him. What responsibilities does the administration have in relation to Jones' behavior? Defend your answer.

Case: Sharing in the Laboratory Setting

Al Glantz has recently completed a successful thesis defense and is planning for his move across the country to his new laboratory. He arranged a meeting with his mentor and lab chief, Calvin Jones.

Al: I'm really grateful for your support over these five years. I learned a great deal. The lab environment was terrific and your recommendation, I'm sure, was instrumental in my obtaining such a promising post-doctorial fellowship.

Prof. Jones: Well, you're one of my best trainees ever and I'm proud of your accomplishments and have great expectations for you as a scientist.

Al: That's great. I thought that this would be a good time to review some housekeeping details so that I can use my remaining time in the lab most productively.

Prof. Jones: That's a great idea. What do you have in mind?

Al: Well, I need to write a new investigator proposal to the NIH and I want to continue the work I've been doing here. I have some new ideas to pursue. In order to do that, I would like to utilize all our unpublished results as background and preliminary results for the fellowship application and get a letter from you supporting me and indicating that I will have access to all the DNA probes and monoclonal antibodies I prepared for our projects here. Then I'll really be able to get a good start. I want to start on the grant right away. When I get that done, I will get back to completing the papers describing our most recent results.

Prof. Jones: I'm glad we had this chance to get together on this, because we must make plans for your last three months. I would be happy to write you a good letter with regard to your grant proposal. You have a right to describe anything you personally did as preliminary work but you must not use other unpublished results from the laboratory unless they are accepted for publication and you are a co-author.

If I were you, I would write up the papers first because as you know, the data belongs to the lab and when you're gone, if the papers aren't submitted, I'll ask Fred to write them up and he'll be first author.

You will be able to take the monoclonals, cell lines and C-DNA probes that we send out but you will not be able to take any irreplaceable materials. Finally, you are going to a competing lab that shares materials poorly, so your ability to receive material from us will depend on reciprocity. We have others here whose careers need to be built, you know.

Questions:

1. Was Prof. Jones being unfair?
2. Was Al expecting too much?
3. Was Jones statement consistent with NIH rules on sharing?
4. Who owns the data?

Case: Genetics of Psychopathic Behavior

Dr. Brain discovered that a combination of 3 genetic polymorphisms was present in 86% of people who were criminally psychopathic. This combination of traits was present in 6% of the general population. Utilizing PET scanning, he discovered responses to specific scenarios that correlated very highly with criminal behavior. When the data were published, the investigators surmised that the 3 polymorphisms participated in brain development and when they were fully expressed they altered brain structure and function so that distinction of right from wrong was impossible. They thought that the combination of genetic testing and PET to elucidate the expression pattern attributable to the genes might make it possible to determine in advance the chance of recidivism in convicted criminals, that is to predict criminal behavior.

Shortly after publication Dr. Brain and team began to receive requests from prosecutors and defense attorneys to work up their clients to prove that they did or did not have the career criminal trait. Judges requested an evaluation before sentencing and parole boards also expressed interest.

Faced with fixed budgets, child services organizations wanted to screen troubled youths for the recidivist tendency so they could spend less money on these “incorrigibles” and focus their attention on those they might be able to help.

Questions:

1. Is there a problem with the research?
2. Is there a problem with the reporting of the research?
3. The societal responses to the research could have been anticipated. What implications did that have for Dr. Brain and his team?
4. What should Dr. Brain do now?
5. If there were a medication that could reverse the impetus toward antisocial behavior, would that change the answers to any of these questions?

“The use of flawed or incomplete science, and the reliance on scientific predictions beyond what the science is prepared to support, are exactly the kinds of concerns that should be foremost in the public mind when contemplating the potential social impact of predictive technologies or techniques. It is not just in courtrooms that prediction would have an impact, but also in schools, employment, healthcare systems, government investigations, and in other ways that would dwarf usage by the court system. The potential to pigeonhole, to discriminate, and to judge on the basis of test results could result in substantially negative consequences, including the development of a “neuroscientific underclass” denied access to education and other societal benefits on the basis of their neuroscience test results. These concerns parallel the current dialogue around genetics, and some feel the public dialogue around genetics may illuminate some of the promises and pitfalls that could accompany and greater understanding of the brain.

Though a host of possible predilections might be desirable (e.g. tendency to be honest, willingness to follow authority, etc.), the potential for violence is of particular interest and significance. Prediction of violence has already been the subject of neuroscience research, and it will probably continue to interest science as well as the legal system. It is a predictive measure likely both to have tremendous utility and to carry great risk of misuse; and it is likely to cut both ways in criminal law – in mitigation and in marking someone as being predisposed to violence. While violent behavior will probably never be predicted with complete certainty, the likelihood that techniques will be developed

to distinguish those more likely or even very likely to react with violence seems quite enough that those techniques be considered for future research and public discussion.”

(“Neuroscience and the Law,” Professional Ethics Report. 2004: 17, p.2)

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Alpert, J. S., K. I. Shine, et al. (2004). "Task Force 1: The ACCF and AHA codes of conduct in human subjects research." *Journal of the American College of Cardiology* 44(8): 1724.

A set of guidelines for cardiologist-investigators regarding clinical research.

Annas, G. J. (2005). "Family Privacy and Death -- Antigone, War, and Medical Research." *N Engl J Med* 352(5): 501-505.

The article examines the issue of family privacy and death through three distinct cases -- the ban on filming of US casualties in war, Vincent Foster's suicide photos, and Iceland's Health Sector Database. It is applicable to investigators in that it highlights the importance of patient privacy after death. The deceased patient's family rather than the investigator has the right of disclosure if the patient participated in a medical study; this fact makes consent forms and other pre-experiment contracts especially important for research participants.

<http://content.nejm.org/cgi/content/extract/352/5/501>

Bates, B. R., J. A. Lynch, et al. (2005). "Warranted Concerns, Warranted Outlooks: A Focus Group Study Of Public Understandings Of Genetic Research." *Social Science & Medicine* 60(2): 331.

This paper does focus groups on public attitudes toward genetic research and its clinical consequences. It concludes that the public has a reasonable understanding of these in its own terms.

<http://www.sciencedirect.com/science/article/B6VBF-4CSYKDG-2/2/5fe206aeb8afd9dcff74ae19fec7ee9f>

Beckwith, J. (2001). "On the Social Responsibility of Scientists." *Ann Ist Super Sanita*. 37(2):189-94

The author deals with the social responsibility of genetic researchers using the discredited eugenics movement in the early 20th century as the model to show that destructive results can be due to scientific developments. Few geneticists are fully aware of the eugenics movement, which led to labeling some humans as genetically inferior. Many geneticists became proponents of eugenics between 1906 and 1915 (scholarly articles and textbook influences). This paper reviews the horrific history and allows us to project the future. It also goes into the ELSI process in the human genome project and the failures of communication between scientists and those involved in the humanities.

Beecher, H. K. (1966). "Ethics and clinical research." *Bulletin of the World Health Organization* 79(4): 367-72.

This is one of the classics in the field of RCRH in that it points a finger at the unethical aspects of research as carried out at the time.

Benditt, J., et al. (1995). "Conduct in science." *Science* 268(5218): 1705-18.

This is the introduction to a number of papers on the culture of science and the methods for teaching responsible conduct of research. The whole sequence should be required reading of teachers of RCR.

Berry, R. S. (2003). "Validity and Ethics in Science." *Science* 300(5624): 1341-.

The author indicates that in science there are experiments and concepts that can be shown to be wrong by further research and experiments and concepts that are fraudulent, and known by their authors to

be so from the beginning. In dealing with misconduct, science is proposed to distinguish between the two poorly, and that is unsatisfactory.

<http://www.sciencemag.org/cgi/content/summary/300/5624/1341>

Bird, S. J. (1998). "The Role of Professional Societies: Codes of Conduct and Their Enforcement." *Sci Eng Ethics* 4(3): 315-320.

In discussions of professional standards and ethical values it is reasonable to consider who will develop the codes of conduct and guidelines for behavior that will reflect the standards and values of the community. Also worthy of consideration is whether the standards or guidelines are enforceable, and how and to what extent they will be enforced. The development of guidelines or professional codes of conduct is a responsibility that has been adopted by many professional societies. Useful to this discussion is an examination of the rationale behind the development of ethical codes by professional societies. The Ethics in Science Committee of the Council of Scientific Society Presidents (CSSP) has examined the codes of some of its member societies and some observations regarding them are pertinent. The nature and uses of ethical statements, codes and guidelines developed by professional societies are multiple and diverse. Their enforcement raises both practical and ethical concerns.

Block, S. (2002). "A Not-So-Cheap Stunt." *Science* 297(5582): 769-70.

This brief paper describes the de novo synthesis of the polio virus, an exercise in the creation of life from precursors. The article generated considerable concern as a potential blueprint for terrorists and raised questions about the social responsibility of scientists regarding publishing material that could be misused in that way.

<http://www.sciencemag.org/cgi/content/full/297/5582/769b>

Bloom, F. (1995). "Scientific conduct: contrasts on a gray scale." *Science* 268(5218): 1679.

Intense competition for funding and commercial influences on science have made it more difficult for scientists to live up to ethical standards. This is especially true when subtle ethical choices are involved such as deciding whose name will be listed first on a research report.

Blumenthal, D., E. G. Campbell, et al. (1997). "Withholding research results in academic life science. Evidence from a national survey of faculty." *JAMA* 277(15): 1224-1228.

This empirical study of scientists' behavior and the consequences for the progress of science focuses attention on secrecy as a mechanism of enhancing a laboratory's relative position and its consequences for society as a whole. A good study.

Bramstedt, K. and K. Kassimatis (2004). "A study of warning letters issued to institutional review boards by the United States Food and Drug Administration." *Clin Invest Med* 27(6): 316-23.

The author analyzed FDA warning letters to IRBs and found that the most common cause of a letter was failure to follow written procedures as to monitoring research after it was initiated.

Brody, J., D. Scherer, et al. (2003). "Voluntary assent in biomedical research with adolescents: a comparison of parent and adolescent views." *Ethics and Behavior* 13(1): 79-95.

This study tests the relationship between perception of risk/aversion between adolescents with asthma and their parents in relation to an asthma protocol set to test agreement. There was about 75% concordance between the two and each felt that they were in control.

Brown, S. K., M. (1998). "Effects of Training in the Responsible Conduct of Research: A Survey of Graduate Students in Experimental Sciences." *Sci Eng Ethics* 4(4): 487-498.

Do all these courses have an impact? And what is it? Tune in and see.

Campbell, E. G., B. R. Clarridge, et al. (2002). "Data Withholding in Academic Genetics: Evidence From a National Survey." *JAMA* 287(4): 473-480.

The free and open sharing of information, data, and materials regarding published research is vital to the replication of published results, the efficient advancement of science, and the education of students. Yet in daily practice, the ideal of free sharing is often breached. The authors mailed a survey to geneticists and other life scientists in the 100 US universities that received the most funding from the National

Institutes of Health in 1998 with a response rate of 64%. They compared 1240 geneticists with 600 self-identified nongeneticists. There was substantial withholding of data even after publication and loss of scientific efficiency. Those who withheld had various reasons including further need to publish from the data and lack of resources to comply with requests. This illustrates the weakness of collegiality as a value in certain areas of modern science.

<http://jama.ama-assn.org/cgi/content/full/287/4/473>

Caplan, A. (2003). "Is Biomedical Research Too Dangerous to Pursue?" *Science* 303: 1142.

After the problems, often serious associated with biomedical research, the author concludes that it is worthwhile after all. Whew! The arguments in this brief paper are worth a read.

<http://www.sciencemag.org/cgi/content/full/303/5661/1142>

Chalmers, D. P., P. (1998). "Towards a Consensual Culture in the Ethical Review of Research." *Medical Journal of Australia* 168(2): 79-82.

The authors point out that research rules commonly follow some kind of ethical crisis and that this may not be the best way to develop and maintain regulations. They suggest an alternative method derived from the notion of consent of the governed. They also deplore the propensity of review organizations to increase the standards and therefore continually make it harder for investigators. As Australians they use Australia as the example.

Chen, D. and B. Worrall (2006). "Practice-based clinical research and ethical decision making--Part I: deciding whether to incorporate practice-based research into your clinical practice." *Semin Neurol* 26(1): 131-39.

This paper reviews for neurologist practitioners what clinical research is and the pros and cons of incorporating research into their practices. It also points out, with the expansion of clinical research, that they might have to advise their patients about research participation even if they don't do research themselves.

<http://www.thieme-connect.com/DOI/DOI?10.1055/s-2006-933317>

Chen, D. and B. Worrall (2006). "Practice-based clinical research and ethical decision making--Part II: deciding whether to host a particular research study in your practice." *Semin Neurol* 26(1): 140-7.

The second component of the previous article.

Cohen, J. (1995). "Share and Share Alike Isn't Always the Rule in Science." *Science* 268(5218): 1715-8.

This is a component of a series of articles on sharing in science, generally asking whether the hallowed principle of collegiality has lost its force and left us in a dog-eat-dog scientific world.

Cohen, J. (1995). "The culture of credit." *Science* 268(5218): 1706-11.

Scientific ideals call for collaboration and sharing. But in today's competitive scientific enterprise, a tremendous premium is placed on individual credit, setting the stage for conflict.

Cottingham, K. (2001). "University-Industry Collaborations: Whose Data?" *Science* 11(27).

This ethics case discussion relates to a PhD candidate who participated in a clinical trial as part of her research and found that she could not publish the data as part of her thesis. Because the results were not favorable, she was forbidden to use the data. Three "experts" discussed the scenario.

Cournand, A. (1977). "The Code of the Scientist and Its Relationship to Ethics." *Science* 198(4318): 699-705.

Scientist's norms (principally honesty, objectivity, tolerance, doubt of certitude, and unselfish engagement) are in danger of serious distortion unless broadened to apply to the relations between scientists and nonscientists. Also needing supplementation is an ethic of development appropriate to a fast-changing society and advanced as an approach to the more effective and humane regulation of cultural and technological development. Taken together, furthermore, they indicate the possibility of a humane world order based on the cooperation of a community of scientists and its public. See the date. This nobelist visualized a world that hasn't arrived and may never arrive, considering what humans are. This is a classic.

Couzin, J. (2002). "BIOTERRORISM: A Call for Restraint on Biological Data." *Science* 297(5582): 749-751.

This response to the increasing power of biological sciences suggests that information that might be of use to terrorists not be published in usable form. Others argued that the development of counter weapons depends on knowing what can be done. Needless to say, journals are watching what they print.

Curfman, G. D. and J. M. Drazen (2001). "Too Close to Call." *N Engl J Med* 345(11): 832.

In response to criticism, the NEJM developed a new process for editorial review of papers derived from their own editorial board.

<http://content.nejm.org/cgi/content/extract/345/11/832>

Davidoff, F. (2001). "Sponsorship, Authorship, and Accountability." *N Engl J Med* 345(11): 825-7.

Davidoff, F., C. D. DeAngelis, et al. (2001). "Sponsorship, Authorship, and Accountability." *Ann Intern Med* 135(6): 463-466.

This article, which was published simultaneously in the agreeing journals began the process of improving the status of articles derived from clinical trials sponsored by pharmaceutical companies by making the listed authors understand they are accountable for the contents and should see the underlying data and actually write the paper. Changes in journal review practices as well as entering clinical trials at the beginning in a database as a criterion for publishability are all derived from the meeting of publishers that led to this paper.

<http://jama.ama-assn.org/cgi/content/full/286/10/1232>

Davis, L. L., M. S. Little, et al. (1997). "The Art and Angst of the Mentoring Relationship." *Acad. Psychiatry* 21(2): 61-71.

The authors review the ancient mentoring relationship in Homer's *Odyssey* and the mentoring discourse of Socrates. These relationships illustrate the art of inspiring a searching quality in the subject and the angst of the struggle that accompanies perplexity and unknowing. The developmental stages of the mentor and resident in psychiatric training are reviewed. A number of teaching interventions are discussed as they might be perceived by the student. Finally, Plato's "Allegory of the Cave" is used as a metaphor for the art of enlightenment and angst of learning and teaching in the mentoring relationship.

Dickenson, D. and J. Ferguson (2005). "Advisory Document for Retained Organs Commission." University of Birmingham, UK: Centre for Global Ethics.

This document addresses the burning issue of retained organs and the rights of donors. They suggest a modified property rights approach to regulation of the practice.

http://www.globalethics.bham.ac.uk/consultancy/Retained_organ.htm

Easterbrook, G. (1997). "SCIENTIFIC COMMUNITY: Science and God: A Warming Trend?" *Science* 277(5328): 890-893.

This is a thoughtful discussion of the relationships or the lack thereof between religion and science. Both approaches to the world seek truth in different ways and both exert great power. The question is whether they can be reconciled. Lots of ideas are presented in a vigorous format.

Eastwood, S. D., P; Leash, E; Odrway, S. (1996). "Ethical Issues in Biomedical Research: Perception and Practices of Postdoctoral Research Fellows Responding to a Survey." *Sci Eng Ethics* 2(1): 89-114.

This empirical study surveyed 1005 trainees and got 1/3 to respond. Their ethics were not very strong and it didn't matter whether they had taken training in research ethics during their training. This is well worth reading.

Emanuel, E. J., D. Wendler, et al. (2000). "What Makes Clinical Research Ethical?" *JAMA* 283(20): 2701-2711.

The authors point out that just getting informed consent does not make clinical research ethical. They propose 7 requirements for ethical clinical studies: "(1) value--enhancements of health or knowledge must be derived from the research; (2) scientific validity--the research must be methodologically rigorous; (3) fair subject selection--scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion

criteria for individual subjects; (4) favorable risk-benefit ratio--within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review--unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent--individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects--subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored." They claim that fulfilling all 7 is necessary and sufficient to make clinical research ethical. While studies must be adapted to the environment in which they are conducted, the 7 standards are broad enough to encompass them all. The latter may be questionable but the paper has become an instant classic and clinical research proposals are being evaluated on the basis of the seven points. A must read.

<http://jama.ama-assn.org/cgi/content/full/283/20/2701>

Endocrine Society. (2005). Ethical Guidelines for Research, found on their web site.

An important guide for understanding the basic requirements of publication in an accredited journal. Also a good source for authors looking for a guide to complying with standards of publication. www.endocrinesociety.org

Evans, M., M. Robling, et al. (2002). "It Doesn't Cost Anything Just To Ask, Does It? The Ethics Of Questionnaire-Based Research." *J Med Ethics* 28(1): 41-44.

This paper presents an analysis of potential psychological forms associated with questionnaire research, using as the example a study of attitudes toward breast disease in English women. They point out the possibility of harm both to researchers and to the practicing physicians cooperating in the study.

<http://jme.bmjournals.com/cgi/content/full/28/1/41>

Faigman, D. L. (2002). "SCIENCE AND THE LAW: Is Science Different for Lawyers?" *Science* 297(5580): 339-340.

The author argues that the law is suspicious of the scientific method as a source of expertise. One of the reasons is that in contentious cases the science may not be there, but there is also the underlying theme that probabilistic thinking is difficult for the law. They discuss criteria for credibility of scientific information.

Ferber, D. (2004). "Occupational health. Beset by lawsuits, IBM blocks a study that used its data." *Science* 304(5673): 937-9.

This article deals with internal IBM data that might show an increased mortality rate in certain IBM work categories. The data were not part of a systematic study and, as they were the subject of numerous torts, they refused to allow the data to be utilized and promised a new, proper study.

Fine, M. K., L. (1993). "Reflections on Determining Authorship Credit and Authorship Order on Faculty-Student Collaborations." *American Psychologist* 48(11): 1141-1147.

This think piece focusing on psychology, reviews various kinds of trainee-faculty relationships in performing and reporting research. They indicate that beneficence, justice and paternalism should apply in making the decisions.

Flanagin, A., P. B. Fontanarosa, et al. (2002). "Authorship for Research Groups." *JAMA* 288(24): 3166-3168.

This editorial tries to adopt fair policies for the listing of authors in large multicenter clinical trials. They recognize that it's a tricky matter both to determine who meets authorship criteria and to properly credit those who are not lead authors.

<http://jama.ama-assn.org/cgi/content/full/288/24/3166>

Francke, U. (1999). Response to National Bioethics Advisory Commission on the Ethical Issues and Policy Concerns Surrounding Research Using Human Biological Materials. H. T. M. Shapiro, Eric. Meslin.

These authors, officers of the Am. Soc. For Human Genetics comment very negatively on the proposals of the NBAC regarding the use of human biological materials. The most powerful objections are

to the absolute requirement for anonymization and for revisiting donors to get permission to use their materials for new projects. They claim it will bring certain types of science to a halt.

Garland, B. (2004). "Neuroscience and the Law." Professional Ethics Report 17(1).

This reports on a conference that eventually became a book relating primarily to 4 questions. How will ability to predict behavior alter the law? How will scientific lie detection affect testifying witnesses? How could new neurological knowledge affect discrimination? What are the risks and benefits of brain modification for enhancement? These questions address key ethical issues including "free will" and responsibility for behavior.

Goodman, Ellen (2001). Medicine needs more "chumps". Boston Globe. Boston, MA. March 1, 2001.

In her way she points out that those who did not benefit financially from their discoveries were, perhaps, better off and more respected than those who struggle to make the last entrepreneurial dollar from their scientific achievements.

Goodwin, F. M., A. (1999). "Scientists in Bunkers: How Appeasement of "Animal Rights" Activism Has Failed." The Dana Forum on Brain Science 1(2): 50-62.

These investigators argue that appeasing animal rights activists only encourages them to demand more and more. They will never be satisfied. The suggestion is pushing back.

Gray, M. L. and J. V. Bonventre (2002). "Training PhD researchers to translate science to clinical medicine: Closing the gap from the other side." Nat Med 8(5): 433.

The authors suggest that training basic scientists to have a more practical bent and become interested in translational medicine will more discoveries to the pharmacopoeia

Grinnell, F. (1999). "Ambiguity, trust, and the responsible conduct of research." Sci Eng Ethics 5(2): 205-14.

Ambiguity associated with everyday practice of science has made it difficult to reach a consensus on how to define misconduct in science. This essay outlines some of the important ambiguities of practice such as distinguishing data from noise, deciding whether results falsify a hypothesis, and converting research into research publications. The problem of ambiguity is further compounded by the prior intellectual commitments inherent in choosing problems and in dealing with the skepticism of one's colleagues. To do this responsibly, the underlying theme had to be trust. However, in today's environment trust had to be earned by being a responsible investigator. This paper raises lots of issues distinguishing the reality of scientific endeavor from the theoretical.

Grunberg, S. M. and W. T. Cefalu (2003). "The Integral Role of Clinical Research in Clinical Care." N Engl J Med 348(14): 1386-1388.

This article analyzes the relationship between clinical care and research in the performance of therapeutic clinical research. They argue that the role of the physician cannot be abrogated during the course of research and that individual subject improvement is the goal. This paper is very well worth reading in the face of contrary arguments indicating that researchers cannot put themselves in the position of clinicians if they are to conduct the research properly.

Gupta, M. (2003). "A Critical Appraisal Of Evidence-Based Medicine: Some Ethical Considerations." Journal of Evaluation in Clinical Practice 9(2): 111-121.

This paper analyzes the philosophical support for "evidence-based medicine" as the route to better health care, focusing on the intrinsic weaknesses of the data and biases in the research.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2753.2003.00382.x>

Gwynne, P. (1999). "Corporate Collaborations." The Scientist 13(11): 1, 6.

The reporter discusses cases in which a scientist under a confidentiality clause was prevented from reporting on adverse events associated with the research. This occurred under conditions under which the institution did not insist on academic freedom. The importance of writing the right kind of contract with industry was emphasized.

Helmuth, L. (2001). "COGNITIVE NEUROSCIENCE: Moral Reasoning Relies on Emotion." *Science* 293(5537): 1971a-1972.

This short paper demonstrates that what we consider to be moral reasoning is not fixed in the rational brain but is associated with feeling developed by the manner in which the information is presented to us.

Hensley, S. and L. Abboud (2004). Medical Research Has 'Black Hole.' Negative Results Often Fail to Get Published in Journals; Some blame Drug Industry. *Wall St J.* New York: B3. June 5, 2004.

This well-written article brings into focus the problems associated with failure to publish negative reports, something that has since gotten a great deal of attention.

Hoeyer, K., L. Dahlager, et al. (2005). "Conflicting notions of research ethics: The mutually challenging traditions of social scientists and medical researchers." *Social Science & Medicine* 61(8): 1741.

When anthropologists and sociologists try to study health services in medical institutions, serious problems arise that are proposed in this paper to be due to cultural differences that might be ameliorated by dialogue. Good luck!

<http://www.sciencedirect.com/science/article/B6VBF-4G1GFK2-1/2/3b6968c880005504c1256540aaff920>

Inouye, S. K. and D. A. Fiellin (2005). "An Evidence-Based Guide to Writing Grant Proposals for Clinical Research." *Ann Intern Med* 142(4): 274-282.

The competition for research funding is intense. Patient-oriented research lags in support behind that allocated for basic science research. Much of the time that is due to poor experimental design and poor grant-writing, neither of which are taught to M.D.s. This article gives an outline for the grant-writing process for clinical researchers. It focuses on those components of the grant proposal that are most likely to be criticized. They recommend methods to improve the quality of areas commonly cited as deficient. This is a really neat paper for anyone in the early phases of a career who has to write and write in hopes of getting funded.

Institute of Medicine. (2002). *Responsible Research: A Systems Approach to Protecting Research Participants*.

This book attempts to describe improvements to the entire process of clinical research, emphasizing the protection of vulnerable participants. It makes numerous recommendations to institutions and government to improve the research process and better prepare all the team members for their roles. It should be required reading for those who have institutional responsibility for research.

Kaiser, J. (2005). "SCIENTIFIC PUBLISHING: NIH Wants Public Access to Papers 'As Soon As Possible'." *Science* 307(5711): 825-.

The NIH has pushed for early online access to research papers and manuscripts in order to increase public awareness and knowledge about science. However, publishers have battled against early release, since giving free access would significantly decrease revenues from scientific journals and reduce funds available to scientific organizations. The article contrasts pressure to make new research studies available with the pressure to produce sufficient revenues to preserve vital scientific organizations. It is significant in addressing both of these issues in an objective way.

Kempner, J., C. S. Perlis, et al. (2005). "ETHICS: Forbidden Knowledge." *Science* 307(5711): 854-.

A discussion of new social and political constraints placed on certain research subject areas. The article focuses on studies that seek to find out how research limitations affect the performance and opinion of scientists. Although most agreed that social constraints offered important protection for patients, many scientists felt uncomfortable with policy-makers setting limitations on their research. The article addresses the responsibility of investigators to maintain social norms while attempting to produce novel research.

Kennedy, D. (2001). "Editorial: "Accepted Community Standards"." *Science* 291(5505): 789.

This editorial deals with the concept that readership should have access to all the materials necessary to replicate a paper should they be skilled enough to do it. However, as science has become more proprietary and complex there has been movement away from this standard. He reiterates the standard and discusses exceptions.

Kennedy, D. (2003). "Multiple Authors, Multiple Problems." *Science* 301(5634): 733.

The author of this editorial deals with the problem of identifying the person among many authors who was responsible for problems in a paper and with the problem of promotion committees deciding whether an author made a critical contribution or otherwise. He suggests that authors be asked to identify their role in each paper.

Korenman, S. G., R. Berk, et al. (1998). "Evaluation of the Research Norms of Scientists and Administrators Responsible for Academic Research Integrity." *JAMA* 279(1): 41-47.

This study used a sophisticated scenario matrix method with 12 scenarios in four domains of research ethics to examine the professional norms of basic molecular and cellular biologists and institutional representatives to whom they were responsible. There was a 69% response rate. The investigators found that both groups expressed a high degree of research integrity and there was a hierarchy of research malfeasance with fabrication and plagiarism on the top. While scientists and institutional representatives expressed similar normative values, they differed significantly in their approaches to an unethical act.

Leshner, A. I. (2005). "Where Science Meets Society." *Science* 307(5711): 815-.

This article examines the clash between social/moral value-systems and advances in research. It attempts to examine ethical boundaries to scientific research within the framework of modern society; however, the article does not make a decisive conclusion on the value of ethical limitations on research.

Madsen, S. M., M. R. Mirza, et al. (2002). "Attitudes Towards Clinical Research Amongst Participants And Nonparticipants." *Journal of Internal Medicine* 251(2): 156-168.

This Danish study showed that subjects and potential subjects have a positive attitude toward research. Those entering studies do it for both personal and altruistic reasons and those who refuse to participate were concerned about the unknown and about randomization.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2796.2002.00949.x>

Marshall, E. (2002). "DATA SHARING: Clear-Cut Publication Rules Prove Elusive." *Science* 295(5560): 1625.

This comments on problems associated with producing a uniform code on the ethics of publishing as discovered at a meeting for that purpose. Again it was associated with the issues surrounding data sharing.

May, R. M. (2001). "Science and Society." *Science* 292(5519): 1021.

He discusses a number of ways in which society is puzzled and disappointed by science, especially since science usually has many voices with different agendas in issues of interest to the public. An example is how to handle bovine spongiform encephalopathy in England.

Merton, R. (1942). "A note on Science and Democracy." *J Legal and Political Sociol* 1: 115-126.

This little classic laid out the underlying responsibilities of scientists, to seek the truth with objectivity, to share, and to self-govern.

Michels, R. (1999). "Are Research Ethics Bad for Our Mental Health?" *N Engl J Med* 340(18): 1427-1430.

The author argues that many important mental health studies cannot be done because of the rules requiring informed consent. He points out the importance of studying the most serious psychiatric illnesses and the difficulty getting approval for the research. This continues to be a minority viewpoint.

Miller, F. G. and D. L. Rosenstein (2003). "The Therapeutic Orientation to Clinical Trials." *N Engl J Med* 348(14): 1383-1386.

Considers the ethical differences between clinical care and clinical research and argues that they should be more separated. Discusses in relation to the "Therapeutic misconception." Excellent Bibliography.

Miller, F. G., D. L. Rosenstein, et al. (1998). "Professional Integrity in Clinical Research." *JAMA* 280(16): 1449-1454.

This excellent paper considers the dilemmas inherent in the physician carrying out clinical research. Although it notes the importance of regulation it focuses on the role of professional integrity in both halves of the clinical investigator role. They perform a critical examination of the moral identity of physicians as practitioners and as scientists and points out that they are indeed different. They show that you can't give up your responsibility as a physician completely when you carry out research. Nicely done arguments.

Miller, F. G. (2002). "Ethical Significance of Ethics-Related Empirical Research." *J Natl Cancer Inst* 94(24): 1821-1822.

This editorial comments on an empirical study of oncologists' understanding of trials in which they participate. The author supports the idea of empirical ethics research and points out that it too can be excellent on trivial, well or poorly done.

<http://jncicancerspectrum.oxfordjournals.org/cgi/content/full/jnci;94/24/1821>

Miller, H. I. (2003). "Trickle-Down R&D and the Public Good." *The Scientist* 17(10): 18.

Curing the public-health ills of less-developed countries might be delivered most efficiently by the work that trickles down from the wealthier countries' high-powered research machines.

Morgan, J. P. (2002). "Lessons From a Horse Named Jim: A Clinical Trials Manual From the Duke Clinical Research Institute." *JAMA* 288(8): 1017-1018.

This review of Liu and Davis' clinical trials manual indicates that the book is very readable. It gives an excellent history of the sad story that led to today's clinical research environment and provides useful materials for anyone who wants to engage in clinical investigation.

N.I.H. (2003). Final NIH Statement on Sharing Research Data. N.I.H.

The NIH comes down on the side of data sharing and has the capability to make it happen.

Nathan, D. G. (2002). "Careers in translational clinical research-historical perspectives, future challenges." *JAMA* 287(18): 2424-7.

The author lays out the problems with developing a career in translational research under the funding mechanisms as they exist and the promotion policies of academic medical centers.

Petrelli, N. J. (2002). "Clinical Trials Are Mandatory for Improving Surgical Cancer Care." *JAMA* 287(3): 377-378.

The author notes that many advances in surgery have not gone through a formal clinical research process to their detriment. He argues that formal clinical trials are needed in surgical oncology.

Phillips, R. L., C. Jim, et al. (2004). "Intellectual Property Rights and the Public Good. Universities have Obligations To Developing Countries." *The Scientist* 18(14): 8.

Is there a fiduciary responsibility of academic institutions to provide patented materials to poor countries? They use the example of Golden rice, which would save many from blindness but is hung up in private hands and beyond the ability of the poor to pay.

Porter, R. and V. Tech (2003). "Facilitating Proposal Development: Helping Faculty Avoid Common Pitfalls." *The Journal of Research Administration* XXXIV(1): 28-32.

With increasing pressure to obtain extramural funding, success in proposal writing becomes ever more important to colleges and universities. Though the characteristics of good proposal writing are well understood, success ratios remain low and most proposals are rejected on first reading. This paper discusses the dimensions of the problems, identifies some common proposal errors and pitfalls, and suggests techniques to avert them. It concludes that grants specialists can employ intervention strategies centered around internal competitors, early career award workshops, funding search workshops and acceptance of pre-proposals to help faculty improve their grant writing skills.

Price, J., J. Dake, et al. (2001). "Selected ethical issues in research and publication: perceptions of health education faculty." *Health Education & Behavior* 28(1): 51-64.

This paper surveys a random sample of health education faculty with regard to their perceptions of ethical issues in research and publishing. Most of the respondents were academically mature. They were asked to rate whether each of 21 scenarios was ethical, unethical, questionable or not an ethical issue. The responses were overall quite variable but this did not relate to rank, gender or other demographic factors..

Reinhardt, U. E. (2004). "MEDICINE: Health Care in the Service of Science?" *Science* 303(5664): 1613-1614.

This review of Daniel Callahan's book "What Price Better Health", that argues that hell-bent scientific development is not the most effective way to optimize health in the population. He feels that scientists have a social responsibility to direct their research where they could reasonably think it will do the most medical good. Reinhardt believes that the way we do medicine reflects societal values and that Callahan is a little off track. Very good reading.

Rennie, D. (2004). "Trial Registration: A Great Idea Switches From Ignored to Irresistible." *JAMA* 292(11): 1359-1362.

The author reviews the recent history leading to clinical trial registration. Required reading.

Rensberger, B. (2000). "ESSAYS ON SCIENCE AND SOCIETY: The Nature of Evidence." *Science* 289(5476): 6.

The author, a science writer, responds to criticisms of his profession that they do not teach Americans about science and that opposition to science is based on their giving equal space to quacks as to real science, by indicating that the quality of scientific evidence is often very weak, generating doubt on its own. A very good short paper about the weakness of scientific communication.

Roberts, L. W., T. Warner, et al. (2003). "What is ethically important in clinical research? A preliminary study of attitudes of 73 psychiatric faculty and residents." *Schizophrenia Bulletin* 29(3): 607-13.

This survey of psychiatric faculty and residents at one facility identified scientific quality and safeguards followed by trust in the integrity of the PI as the most important ethical aspects of clinical research. As might be expected, the residents are more ethically sensitive than the faculty.

Rodbard, D., P. O'Shea, et al. (2003). Survey of Research Integrity Measures Utilized in Biomedical Research Laboratories. American Institutes for Research.

This private survey conducted for the NIH identified methods that scientists think preserve research integrity and the kinds and duration of training activity in research integrity.

Rosenberg, L. E. (1999). "Physician-Scientist- Endangered and Essential." *Science* 283: 331-332.

The author raises the alarm about the declining number of physicians preparing themselves as scientists and doing clinically related research. This argument was heard, finally in 2006.

Sa Couto Md, J. (2003). "An Objectivist's View On The Ethics Of Evidence-Based Medicine: Commentary On 'A Critical Appraisal Of Evidence-Based Medicine: Some Ethical Considerations' (Gupta 2003; *Journal of Evaluation in Clinical Practice* 9, 111-121)." *Journal of Evaluation in Clinical Practice* 9(2): 137-139.

The author constructs a strong argument that "evidence-based medicine" and reason based on medical theory are incompatible. This "evidence based medicine" is opposed to objective reason. <http://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2753.2003.00401.x>

Saletan, W. (2001) The Ethicist's New Clothes. Slate Volume, DOI:

This article points out that drug and device companies were hiring ethicists as consultants, and compromising them. The ethicists seemed to them to be blind to how bad their conflicts of interests were in their field of endeavor.

Schacter, B. (2002). "Partners in Research, Competitors in Pay." *The Scientist* (March 4, 2002): 44-45.

The author sheds light on the fact that while scientists collaborate broadly in research, they are really competitors for the same relatively few good positions and pay. He points out the irony in this. But, is this so different from the real world where leadership teams both collaborate and compete?

Sideris, L., C. McCarthy, et al. (1999). "Roots of Concern with Nonhuman Animals in Biomedical Ethics." *ILAR Journal* 40(1): 3-14.

This paper reviews the history of concern for research animals and the impact of passionate anti animal research groups in getting more humane treatment of research animals on the regulatory agenda.

Silbergeld, E., S. Lerman, et al. (2004). "ETHICS: Human Health Research Ethics." *Science* 305(5686): 949-.

This is a strong argument for the use the "common rule" in designing and carrying out studies related to environmental protection. Distinctions between internal EPA studies and non-governmental studies that exist are proposed for change.

Steinbrook, R. (2000). "Medical Journals and Medical Reporting." *N Engl J Med* 342(22): 1668-167.

The author defends the role of the NEJM in reporting materials to the media. They claim purity because they only send out an advance copy of each issue to the press. Of course, we subscribers believe we are paying for the first look at the information. A very self-serving article, I think.

Steinbrook, R. (2004). "Public Registration of Clinical Trials." *N Engl J Med* 351(4): 315-317.

This is one of the articles from leading journals that publish clinical trials arguing the importance of registration. Subsequently, registration has become essentially required.

Swazey, J. P., M. S. Anderson, et al. (1993). "Ethical Problems in Academic Research: A survey of doctoral candidates and faculty raises important questions about the ethical environment of graduate education and research." *American Scientist* 81: 542-553.

This empirical study of faculty and trainees indicated that ethical lapses were both commonly admitted and commonly noted in others. The authors argued for better ethical education.

Tunis, S. R., D. B. Stryer, et al. (2003). "Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy." *JAMA* 290(12): 1624-1632.

This policy proposal argues that we need much greater emphasis in research on practical clinical trials to help medical decisions makers make rational choices or offer rational choices to their patients. Almost all current clinical trials are designed for different purposes and are not helpful in real decisions <http://jama.ama-assn.org/cgi/content/full/290/12/1624>

Vandenbroucke, J. P. (2001). "In Defense of Case Reports and Case Series." *Ann Intern Med* 134(4): 330-334.

The author argues that case reports and case series have their own role in the progress of medical science. They permit reporting of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. He claims that case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress. Good case reporting demands a clear focus to make explicit to the audience why a particular observation is important in the context of existing knowledge.

Varki, A. and L. E. Rosenberg (2002). "Emerging opportunities and career paths for the young physician-scientist." *Nat Med* 8(5): 437.

The authors trumpet careers in translational medicine for scientifically trained physicians.

Wallerstein, M. B. (2002). "Science in an Age of Terrorism." *Science* 297(5590): 2169.

The author suggests that to thwart the use of biological agents by terrorists, we have to be careful in specific sensitive areas and try to teach our foreign students and other trainees to use what they learned for good. Sounds good but ...

Wenger, N. S., S. Korenman, et al. (1997). "The ethics of scientific research: an analysis of focus groups of scientists and institutional representatives." *J Investigative Med* 45(6): 371-80.

The authors report on the range and depth of perceptions of scientists and institutional representatives on what is unethical in science.

Wolpert, L. (1989). "The social responsibility of scientists: moonshine and morals." *BMJ* 298(6678): 941-3.

A very compelling article that contrasts research for the Manhattan project with the eugenics movement leading to 1930s Nazi policy of discrimination and genocide. While the designers of the atomic bomb are praised for their insight, the eugenics movement is now seen as one of science's greatest evils. The author concludes that scientists must have the capacity to research all fields, but also bear the responsibility of disclosing the ramifications of their research.

Yarborough, M. and R. Sharp (2002). "Restoring and preserving trust in biomedical research." *Acad Med* 77(1): 8-14.

This significant position paper describes the diminution of trust in clinical research associated with recent events and the media characterization of them. The authors argue that if these institutions are to preserve the trust that the public has historically bestowed upon them, they must go beyond mere compliance with regulatory mandates. Several steps are suggested that the authors believe will bolster the public's confidence in academic research institutions. These steps grow out of the authors' analysis of three key components of institutional trustworthiness: (1) shared goals between research institutions and the communities they serve, (2) robust institutional oversight of research activities, and (3) training programs that build professional character. The authors' recommendations include the use of research advisory councils to assure the public that research goals reflect community interests, more collaborative relationships between institutional review boards and members of investigative teams, and educational programs that emphasize the importance of professional integrity in biomedical research.

Zigmond, M. (1999). "Promoting responsible conduct: striving for change rather than consensus. Commentary on "Ambiguity, trust, and the responsible conduct of research" (F. Grinnell)." *Sci Eng Ethics* 5(2): 219-28.

In this paper the author duels with Fred Grinnell about promoting the responsible conduct of research. He points out that "aspirational codes depend too much on the individual. He thinks that discussion and controversy play a role in buy in and clarification of issues and, unlike Grinnell, the scientific societies and investigators should play an important role in defining the rules of behavior. This is a very worthwhile read for those interested in teaching the responsible conduct of research.

Chapter 2 Research in humans

Research in humans differs from other research in that the subject has decision-making power and must be treated with respect. The long history, even in the name of science of one group of humans exploiting another has made it necessary to establish elaborate rules and procedures to protect human participants in research.

A. History of rules about research in humans

The Nuremberg Code 1947

“The great weight of evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts.”

Ten principles were then enunciated

(<http://www.ushmm.org/research/doctors/codeptx.htm>)

These have been condensed to:

- 1. Autonomy – voluntary informed consent**
- 2. Beneficence – good science and favorable benefit to risk ratio**
- 3. Justice – equal opportunity to participate and to not participate**

The investigator was given the responsibility for seeing to it that the ethical requirements were met.

The World Medical Association developed the Declaration of Helsinki, first in 1964.

It has been amended repeatedly since then.

<http://www.wma.net/e/policy/b3.htm>

Ethical Principles for Medical Research Involving Human Subjects

Thirty-two statements are made in the Declaration including (in paraphrase)

- 1. The primary responsibility of physicians is the best care and research is secondary.**
- 2. Research is important to improve health care**

3. Investigators should be aware of the ethical, legal and regulatory requirements for research on humans.
4. Research on humans must be scientifically sound and carried out by qualified persons.
5. It must be voluntary and informed, with consent and ability to withdraw documented.
6. Vulnerable populations may require surrogate consent.
7. The research protocol must have been scrutinized and approved by an ethics committee for risks and benefits with minimization of the former and maximization of the latter.
8. Investigators must monitor their research and report problems.
9. The population studied should have a reasonable chance of benefiting from the results.
10. Reporting and publication should adhere to the facts.
11. A limitation was placed on jointly providing clinical care and research.
12. Placebo use was strictly limited. Investigators should try to compare standard of care with the new agent.

The Belmont Report 1979

(<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/Belmont.htm>)

This report was the culmination of the work of a national commission that began in 1974. It was adopted by the NIH in its entirety and became the basis for institutional arrangements with the NIH to review, evaluate and monitor research on humans. Its main provisions are as follows:

B. Definitions

Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. 45 CFR 46.102(d)

Human Subject

A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. 45 CFR 46.102(f)

Intervention:

Physical procedures and manipulations of the subject's environment performed for research purposes.

Interaction:

Interaction includes communication or interpersonal contact between investigator and subject.

Private Information:

Private information is information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, as well as information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

Definition of Human Research

Data from living individuals

Biological material from living individuals

Interaction or intervention with a living individual

Use of a non-FDA approved, drug, device or biological

C. Federal Mandate

I direct each department and agency of Government to review present practices to assure compliance with the Federal policy for the Protection of Human Subjects and to cease immediately sponsoring or conducting any experiments involving humans that do not fully comply with the Federal Policy.

President Bill Clinton

D. Respect for persons

Choices of autonomous individuals should be respected. People incapable of making their own choices should be protected

Respect for persons in clinical research and verification of that respect depend on administration of and signatures on a formal informed consent document. Having taken on the characteristics of an educational, legal, and accountability document, the typical consent form can have 19 items, requires over ten typed pages, and is frequently signed without a full understanding of its terms. In fact often it fails to educate, to protect legally and to function as an auditing tool.

What An Informed Consent Document Must Cover

1. Purpose of the study	10. Financial obligation
2. Procedures	11. Emergency care and compensation for injury
3. Potential risks and discomforts	12. Privacy and confidentiality
4. Anticipated benefits to subjects	13. Participation and withdrawal
5. Anticipated benefits to society	14. Consequences of withdrawal
6. Alternatives to participation	15. Withdrawal of participation by the investigator
7. Payment for participation	16. New findings
8. Possible commercial products	17. Identification of investigators
9. Sample remaining at the end of the study	18. Rights of research subjects
	19. HIPAA privacy rights

The informed consent document operates largely to define institutional policies and the features of an individual protocol. Recent catastrophic delinquencies in consent forms have led to a general tightening of the process with questionable effects on educational capacity and legal protections. The required paragraph for HIPAA may add to the confusion.

Whatever the weaknesses of the formal consent process, the PI as a fiduciary for the subject, retains the responsibility to explain the rationale and content of the study in such a manner and for a sufficient time so that participants understand it and give fully informed consent.

The consent must also be voluntary. Coerced consent, expressed or implied, may occur under a number of circumstances including: when participation is a contingency for treatment, when enough payment is made to constitute an inducement, when the subject is really not a free agent, (e.g. prisoners and dependent children, or members of cultures where decisions are centralized).

The investigative team must be reasonably sure that surrogates consenting for impaired or underage subjects are fulfilling their fiduciary responsibility to the subjects.

D. Beneficence

Clinical research protocols should be designed to maximize the benefits to an individual or to society while minimizing harm to the individual. But in research we do not know in advance all the harms that may occur, so we must monitor and stop the research should harms become significant in comparison to the benefits. We also do not know in advance to what extent the benefits greatly exceed the alternative so that the randomization must be stopped. Thus, the ethical decisions of data and safety monitoring boards regarding continuation of trials have become important elements of beneficence.

E. Justice

Distributive justice means the equitable distribution of the burdens and benefits of research. Investigators may not exploit vulnerable individuals or exclude without good reason eligible candidates who may benefit from a trial. This is now a federal rule and is monitored for all NIH and FDA clinical trials.

The Belmont report also led to Institutional Review Boards and Multiple Project Assurances of institutions with the Federal Government to carry out ethical evaluation and review of all research considered human research and to monitor the progress of studies. This means local control and local responsibility with Federal oversight.

In 1979 the Federal government adopted the "Common Rule."

F. Common Rule

The Common Rule is a federal policy regarding Human Subjects Protection that applies to 17 Federal agencies and offices. It does not apply to federal agencies that have not signed the agreement (e.g., Department of Labor, etc.) The main elements of the Common Rule include:

Requirements for assuring compliance by research institutions

Requirements for researchers' obtaining and documenting informed consent

Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.

The Common Rule includes additional protections for certain vulnerable research subjects.

Subpart B provides additional protections for pregnant women, in vitro fertilization, and fetuses

Subpart C contains additional protections for prisoners

Subpart D does the same for children.

DHHS Regulations are provided in 45 CFR, Part 46.

http://www.access.gpo.gov/nara/cfr/waisidx_99/45cfr46_99.html

FDA Regulations are detailed in 21 CFR, Part 50, and 21 CFR, Part 56. You can review these at

<http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=199945>

An institution with a DHHS approved Federal Wide Assurance typically agrees to apply DHHS regulations to all research regardless of the funding source, including research that is internally funded and collaborative research across institutions

G. Institutional Review Board (IRB)

IRBs are impaneled to protect the rights and welfare of human subjects and support the institution's research mission. By requiring local review the Federal Government requires local responsibility that is both institutional and individual.

Researchers must respect and protect the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Institution. By institution is meant any entity that is sanctioned by the Federal Government to conduct research. The IRB is constituted to be the agency within the institution that reviews and approves research involving humans. Research actions are guided by the principles set forth in the Belmont report (see above).

IRBs have a full time administrative core to handle the applications, keep abreast of the changing rules, and monitor the approved protocols. IRB members consist of faculty and non-affiliated non-scientists who in the aggregate possess a broad range of expertise and interests corresponding to the research proposed.

Research institutions have a contract, called an assurance, with the Federal government outlining their collective obligations and responsibilities to protect human subjects. These multiple project assurances require ethical review of all human research under defined rules. Review by the institutional IRB(s) is required for research on humans when the conduct or recruitment of the research involves institutional resources, property, or facilities, regardless of funding source, when the research is conducted by or under the direction of any employee, student, or agent of the institution:

**in connection with her/his institutional responsibilities
using any property or facility of the institution
when the research involves the use of an institution's non-public information to
identify or contact potential subjects**

The Common Rule adopted the principle of local control of research oversight because:

It would enhance education of the research community & the public

It would provide greater familiarity with the actual conditions surrounding the conduct of the research

It would enhance the ability to work closely with scientists to assure the protection of the rights and welfare of the subjects

It would assure that the application of policies is fair to investigators

Any study involving research on human beings must go through the IRB. However, there are certain exceptions based on the intent of the research or on the characteristics of the study.

Hospitals are required to carry out programs of quality assurance that involves research into clinical practices in the institution. These are usually designed to improve the care locally and there is no intent to generate generalizable

knowledge. That is not considered research. On the other hand, a program evaluation/quality assurance program becomes research when the intent of the project is to answer a research question or create generalizable knowledge that will be shared outside of the program being assessed, such as journal articles, professional presentations, etc. Frequently the findings precipitate the interest in publishing.

In general, a Study is exempt from IRB Review if it is

Research in commonly accepted educational settings involving normal educational practice (Think course evaluations)

Surveys,

Interviews

Questionnaires

Observation of public behavior, unless subjects can be identified, directly or through identifiers linked to the subjects; and any disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal liability or be damaging to the subjects' financial standing, employability, or reputation

Collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if:

The sources are publicly available, or

If the information is recorded in such a manner that subjects cannot be identified directly or through identifiers linked to the subject

Due to HIPAA: Medical record reviews are no longer exempt

Cases Chapter 2

Case: Phase 1 trials

In the absence of human trials it's impossible to know about the safety of drugs in humans that were found to be safe in other animals. Phase I clinical trials involve the dosing of new drugs to tolerance in control subjects and doing pharmacokinetics to determine blood levels, binding, and disposal rates of the drug.

Years ago, a large drug company advertised for volunteers for Phase I clinical trials of new agents. They noticed as the weather turned cold, middle-aged persons who were dirty and poorly dressed volunteered, and that the number of volunteers increased yearly. The volunteers were housed in a metabolic unit for 6 months and were given a number of agents in sequence during the winter. Each trial was approved by an "in house" IRB. When it became known that many of the volunteers were homeless alcoholics, screening tests were done to ensure that chemistries were normal or near normal. Each volunteer signed a consent indicating that their compensation would be provided to

them at the end of the period of being a control and that they would refrain from alcohol for the duration of their stay.

The company believed sincerely that it was helping these individuals. The process was revealed in the media after some years.

Questions:

1. Was anything untoward happening here?
2. If you believe so, then what was the range of ethical lapses in drug research?

Case: Use Of A Placebo Control

In 2002 a report was published in JAMA describing the results of a trial of sertraline (Zoloft) versus hypericum (St John's Wort) versus placebo in the treatment of severe depression. It was an eight-week trial and all of the subjects were monitored carefully for increased depression or suicidal tendencies at which time they were removed from the trial. Both sertraline and hypericum were no better than placebo. The investigators pointed out that without the placebo group, the conclusion might have been reached that St John's Wort was equally effective as sertraline.

1. Was this an ethical trial? If so, why? If not, why not?
2. Discuss equipoise in clinical research
3. Discuss Geneva Convention and CIOMS guideless for use of placebos
4. Discuss whether clinical research, especially randomized clinical trials require a therapeutic obligation to participants

Case: Tissue Samples

Aortic tissue samples from patients undergoing cardiac transplantation have been collected and stored for many years. Permission for the sampling was granted under the blanket research approval in the surgical consent form. Previously, investigations were permitted under waiver of IRB review because the samples were used completely without identifiers. The samples (n=2000) were dated and stored untouched in liquid nitrogen.

The medical team gave permission to Dr. Gomez, a geneticist, to sample all 2000 specimens to study the prevalence of a number of gene polymorphisms proposed to relate to development of dilational cardiomyopathy. The genetic findings were to be related to a specific patient by identifying the tissue donor by correlating the sample date to the operative schedule. Dr. Gomez claims that no IRB approval or new consent forms were required for this study because the study did not utilize individuals, only stored tissue.

Questions:

1. Are there any limitations on Dr. Gomez' access to the tissues?

2. To perform a complete genetic search, Dr. Gomez would like to provide some of the material to other labs including some commercial labs. Are there any limitations to that?
3. There may be several forms of dilational cardiomyopathy. Dr. Gomez plans to arrange for a cardiology fellow to collaborate and to review all the charts to distinguish between the clinical forms of the condition to further define the genetics. Is there a problem with this?
4. If there are problems how should they be handled?

Case: Alzheimer's

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 I 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?**

Case – Violation of Confidentiality

Researchers cloned and sequenced the gene for Interleukin I. They sent off a paper to Nature, very excited about their great result. Their work was funded by the Cistron Corporation.

A faculty member associated with Immunex had a reviewer on the paper that the above group claims held up the paper and used key information it contained to clone and sequence the same gene.

Even though there never was a market for a product from this gene, Cistron is suing because Immunex got venture capital funding on the basis of the gene and because it became a strong competitor due to that funding. \$100,000,000 is at stake here.

Immunex responded that Cistron had cloned something different, that they were suffering a loss of reputation due to a deliberate misleading reading of the facts and is countersuing.

The core question could turn on what degree of confidentiality is appropriate (the norm) for peer reviews?

Rules have become more explicit. What should they be?

Bibliography Chapters 2

(1953). Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. U. S. G.P.O: 181-4.

(2001). Guidance for Clinical Trials Sponsors: On the Establishment and Operation of Trial Data Monitoring Committees, Food and Drug Administration: 1-19.

(2003). Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. Federal Register. 68: 15456-15460.

(2004). Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. DHHS. Services, Federal Register. 69 (92): 26393-7.

This federal guideline asks IRBs and institutions to consider a variety of means to eliminate, document, disclose, and manage conflicts of interest. It is not overly prescriptive but it expects institutions to actively and effectively deal with conflicts of interest both of individual investigators and of IRB members. Conflict of interest committees distinct from IRBs are expected to be developed. Required reading for research administrators.

The Office of Public Health and Science (OPHS), Department of Health and Human Services (HHS) announces a final guidance document for Institutional Review Boards (IRBs), investigators, research institutions, and other interested parties, entitled Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. This guidance document raises points to consider in determining whether specific financial interests in research could affect the rights and welfare of human subjects, and if so, what actions could be considered to protect those subjects. This guidance applies to human subjects research conducted or supported by HHS or regulated by the Food and Drug Administration.

Anand, G. (2004). Ask Before You Leap: If you're thinking of joining a clinical trial for experimental drugs, make sure to get the answers to these questions. Wall Street Journal. New York. January 26, 2004.

This brief article in the personal section of the WSJ suggests that prospective participants in a clinical trial ask a series of questions including who's in charge? Is there a well-functioning objective IRB? What are the conflicts of interest? And what's actually going to happen to me? Investigators should read this article.

Annas, G. J. (2002). "Medical Privacy and Medical Research -- Judging the New Federal Regulations." N Engl J Med 346(3): 216-220.

There was a lot of worry about the degree to which the HIPAA regulations would inhibit clinical research. It is still a matter of concern but research continues unabated.

Annas, G. J. (2003). "HIPAA Regulations -- A New Era of Medical-Record Privacy?" *N Engl J Med* 348(15): 1486-1490.

This is important in the context of impact on research. The key element is whether the research impinges on the medical chart of the subject. If it does, then all the HIPAA regulations apply. If not then only the research-related common rule applies.

Capron, A. M. (1999). "Ethical and Human-Rights Issues in Research on Mental Disorders That May Affect Decision-Making Capacity." *N Engl J Med* 340(18): 1430-1434.

The author argues that clinical research with a therapeutic intent should have greater oversight than physiological investigation with normal controls because the risk to the subjects is greater in the former than the latter. In mental disorder investigations where informed consent is difficult to achieve, the problem is especially ethically troublesome.

Cohen, J. (1999). "Research Shutdown Roils Los Angeles VA." *Science* 284(5411): 18-19, 21.

This is an example of the issues surrounding appropriate IRB function.

Couzin, J. (2004). "HUMAN SUBJECTS RESEARCH: Pediatric Study of ADHD Drug Draws High-Level Public Review." *Science* 305(5687): 1088a-1089.

This brief news report succinctly reports the very serious ethical problems that arise when attempting to do research with vulnerable populations in this case children employed as control subjects.

Emanuel, E. J., A. Wood, et al. (2004). "Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals." *Ann Intern Med* 141(4): 282-291.

This is a position paper on reform of the IRB system. They identify 15 current problems with the system, including 8 structural, 5 procedural, and 2 performance-assessment. They review suggested reforms and find them not fully corrective of the problems. They then introduce their own set of potential reforms.

Faden, R., S. Lederer, et al. (1996). "US Medical Researchers, the Nuremberg Doctors Trial, and the Nuremberg Code." *JAMA* 276(20): 1667-1671.

These authors reiterate, 50 years later, the impact of the Nuremberg trials documenting Nazi physicians' atrocities and proposing rules about performing research on humans. Clinical research in America and worldwide was designed to protect the rights of the individual subjects' to make uncoerced decisions about participation and to expect that the chance of benefit will generally outweigh the chance of harm. The subsequent research rules in the Belmont report and the Declaration of Helsinki were derived directly from the Nuremberg Report..

Grizzle, W., W. Grody, et al. (1999). "Recommended policies for uses of human tissue in research, education, and quality control." *Arch Pathol Lab Med*. 123(4): 296-300.

As recipients of tissue and medical specimens, pathologists and other medical specialists regard themselves as stewards of patient tissues and consider it their duty to protect the best interests of both the individual patient and the public. The stewardship of slides, blocks, and other materials includes providing, under appropriate circumstances, patient materials for research, education, and quality control. The decision to provide human tissue for such purposes should be based on the specific (i.e., direct patient care) and general (i.e., furthering medical knowledge) interests of the patient and of society. The same standards of responsibility should apply to all medical professionals who receive and use specimens. This document proposes specific recommendations whereby both interests can be fostered safely, ethically, and reasonably.

Gunsalus, C. K. (2003). "Human Subject Regulations: Whom Are We Protecting from What, and Why? Working to Align Incentives with Ethical Goals." *Professional Ethics Report* 16(2)

The author discusses the use of IRBs in research on humans outside of medicine. Social scientists are very concerned about overzealous IRBs severely curtailing what they consider to be harmless research.

In frustration, they engage in "serial mind-reading" trying to produce protocols that will be acceptable to their IRBs. The problem is that IRBs are local and reflect local conditions so investigators are often not sure where they stand. The conference from which this report was generated was to produce a white paper asking for improvements in research regulation.

Halpern, S. D., J. H. T. Karlawish, et al. (2002). "The Continuing Unethical Conduct of Underpowered Clinical Trials." *JAMA* 288(3): 358-362.

This important paper discusses the ethical implications of underpowered clinical trials, indicating that they are becoming more common and have garnered a degree of professional support. They are justified as ways of accumulating data for meta-analyses and for ways of determining efficacy or appropriate dosing. It is unethical to carry out studies on humans in which you can never reach a valid conclusion. It subjects them to risk and bother for no possible reward. Certainly, if that is the intention, participants should know about it and assess the value of their participation. However, clearly, in many cases under powering was not deliberate, but rather the consequence of difficulty recruiting or excessive dropouts. They suggest that underpowered trials are justifiable in treating rare diseases where a meta-analysis will provide statistical validity or in a phase 2 type dosing experiment. Small trials might also be used to develop a protocol. They believe that it is immoral to reach clinical conclusions from inadequate information.

Hawkins, A. (2004). Obligation to human research participants goes far beyond regulatory compliance. Washington Fax. November 4, 2004.

This brief paper tries to answer the claim that today's scientists perceive no obligation to research subjects beyond compliance with the rules. Numerous individuals and government leaders are quoted, all coming to the conclusion that research integrity goes well beyond the rules, but we must have rules. The prevalence of major conflicts of interest mandates the existence of strong regulations.

Henry, R. C. and D. E. Wright (2001). "When Do Medical Students Become Human Subjects of Research? The Case of Program Evaluation." *Acad Med* 76(9): 871-875.

This position paper reviews the ideas behind requiring medical students to fill out graduation questionnaires as an evaluative tool. Are they research subjects when they do this? And if it is required for graduation does that mean that their cooperation in research is coerced? The problem is that the results might be useful to others and therefore subject to publication. Other such "dual purpose activities" include clinical quality assurance studies. The authors conclude that students should know that faculty may publish the results of an educational questionnaire, but they do not go so far as to require the completion of an informed consent document. They do raise the question of when is it appropriate to ask for student consent, thus making the task voluntary.

HHS (2002). Standards for Privacy of Individually Identifiable Health Information--Proposed Rule Modification. U. S. DHS.
<http://www.hipaacomply.com/changetoprivacy.htm>

Humphreys, K., J. Trafton, et al. (2003). "The Cost of Institutional Review Board Procedures in Multicenter Observational Research." *Ann Intern Med* 139(1): 77-.

This short letter examines costs of 9 IRBs and estimates supplemental IRB expenditures at \$56000 per study, after home IRB approval. It chronicles poor communication and fear of punishment as the two main components of over-expenditure. This is a whopping sum that certainly needs to be diminished.

Kaiser, J. (2001). "PATIENT PRIVACY: Researchers Say Rules Are Too Restrictive." *Science* 294(5549): 2070-2071.

This paper reports on the brouhaha associated with the proposed rules for HIPAA, prior to its activation. Some changes were made.

Kaiser, J. (2002). "PATIENT RECORDS: Researchers Welcome Revised Privacy Rules." *Science* 297(5584): 1108b-1109.

The revised HIPAA rules are reported here. It includes a limited data set, which would permit medical record review without identifiability. It also liberalized the time that data could be kept.

www.hhs.gov/ocr/hipaa

Karlawish, J. H. T., D. J. Casarett, et al. (2002). "Alzheimer's Disease Patients' and Caregivers' Capacity, Competency, and Reasons to Enroll in an Early-Phase Alzheimer's Disease Clinical Trial." *J Am Geriatr Soc* 50(12): 2019-2024.

This is a valuable study of small number of persons with early Alzheimer's disease, age matched normal controls and care givers (15 of each). They used the MacArthur Competency Assessment Tool for Clinical Research and audiotaped the interviews for review. They found that all of the controls and 9 of the 15 Alzheimer cases were adjudged to be competent. They conclude that the instrument is very effective in selecting subjects who can sign for themselves rather than have a surrogate sign for them.

Kaufman, J. L., R. Pelligra, et al. (2000). "Protection for Human Subjects in Medical Research." *JAMA* 283(18): 2387-2390.

This is the first of a series of letters to the editor of JAMA regarding the article by Woodward on protection of human research subjects. This supports the review by IRBs that were criticized by the author. Other letters in the group support positions taken by the NBAC, and criticize Dr. Woodward's view that there was movement afoot to weaken protections afforded to research participants.

Korenman, S. and L. Shaker-Irwin (2003). Research Subject Advocacy--A New Way to Enhance Integrity in Clinical Research. *Endocrine Society News*. 1: 6-7.

The National Center for Research Resources provided General Clinical Research Centers funding to recruit and hire individuals to be Research Subject Advocates. The job description was somewhat vague. In this paper the authors describe their response to the charge to advocate for subjects and to oversee their research activities in a constructive manner. This describes how UCLA did it up to the date of the paper. This role has continued to evolve to include much more education, protocol monitoring, and face to face relationships with subjects and the research team.

Korn, D. (2000). "Medical information privacy and the conduct of biomedical research." *Acad Med* 75(10): 963-8.

This constitutes a well thought out and somewhat pessimistic report on the expectations for medical research in the face of HIPAA. He sympathizes with the individual's need for privacy but wonders whether the individual would recognize the substantial benefits to be derived from the availability of medical data for examining and hopes that HIPAA does not close off the road toward chart-base research. By this time, many institutions have found their way to use the chart information needed while not violating HIPAA.

Kulynych, J. and D. Korn (2002). "The New Federal Medical-Privacy Rule." *N Engl J Med* 347(15): 1133-1134.

It examines the new federal privacy rule (*Federal Register* 67: 53182-53273, 2002) by highlighting the differences and going into detail about the costs associated with its inception.
<http://content.nejm.org/cgi/content/full/347/15/1133>

Lehman, C. R., G. (2001). "To IRB or Not to IRB?" *Am J of Clin Pathology* 115(2): 187-191.

This paper, which has become historical by now, deals with the issue of whether pathologists using tissue samples mainly for developing diagnostic test needed IRB approval. At this time, they frequently did not seek such approval and in an empirical study, identifiable tissue samples were often used. I believe that HIPAA has clarified those uncertainties and IRB approval or waiver is necessary when conducting studies of human tissues.

Levine, R. J. (1999). "The Need to Revise the Declaration of Helsinki." *N Engl J Med* 341(7): 531-534.

This position paper reviews the Declaration of Helsinki (since revised) and points out that investigators routinely violate some of the provisions. He also claims that provisions violate contemporary ethical standards. He claims that the Declaration of Helsinki requires revision because it is defective in two important respects. First, it relies on a distinction between therapeutic and nontherapeutic research. Secondly, it includes several provisions that are seriously out of touch with contemporary ethical thinking.

As a consequence, many researchers routinely violate its requirements. Such routine violations and their associated attitudes rob the declaration of its credibility.

Marshall, E. (2000). "BIOMEDICAL ETHICS:HHS Plans to Overhaul Clinical Research Rules." *Science* 288(5470): 1315a-1316.

This report outlines the plans to strengthen the Office of Protection from Research Risks and DHHS. It will also establish serious penalties for clinical investigator lapses and ensure better oversight of research, better deal with conflicts of interest, etc. Strengthening IRBs, one of the goals of the initiative has been carried out but more needs to be done.

Mello, M. M., D. M. Studdert, et al. (2003). "The Rise of Litigation in Human Subjects Research." *Ann Intern Med* 139(1): 40-45.

This is an important paper that identifies the rapidly increasing trend to sue institutions and individuals for bad results associated with clinical research. Litigation will get the profession to examine itself more rigorously, stultifying IRBs and perhaps inhibiting the development of drugs.

Molloy, V. J. and D. R. Mackintosh (2003). "GCP Compliance Problems Encountered at Clinical Sites: Informed Consents, Physical Exams, and Adverse Events." *SoCRA Source*: 12-15.

Nebeker, J. R., P. Barach, et al. (2004). "Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting." *Ann Intern Med* 140(10): 795-801.

Adverse drug events cause substantial morbidity and mortality, yet they remain underappreciated and misunderstood. The terminology to describe errors and patient harm associated with medications causes much confusion. This article uses the case study of a patient with multiple adverse drug events to clarify key terms, such as adverse event, adverse drug reaction, adverse drug event, medication error, and side effect. The case discussion illustrates clinical approaches to analyzing the causal connection between a suspect drug and an adverse event. Examples and rationale for meaningful documentation of adverse drug events are provided, along with an outline of the types of events that should be reported to regulatory agencies.

Partridge, A. H. and E. P. Winer (2002). "Informing Clinical Trial Participants about Study Results." *JAMA* 288(3): 363-365.

Many informed consent forms now indicate that participants will receive information about the results of their trial. That is not always done. This paper addresses the issues involved in that area.

Rising, J., P. Lurie, et al. (2003). Letter to HHS urging a federal investigation of medical schools conducting unethical research.

This letter to Bernard. Shwetz. Acting director of the Office for Human Subject Protections requested that all the medical schools in the US be investigated for requiring seniors to fill out a questionnaire about their medical school experience. These were compiled at the AAMC and utilized by individual schools and the profession to improve its performance. The students objected to the obligatory nature of the response and the failure to obtain consent. The argument was that it was research because someone could study the data and report it although it was intended as an educational quality assurance report. It also pointed out that the seniors would personally derive no benefit from the results.

Shalala, D. (2000). "Protecting Research Subjects -- What Must Be Done." *N Engl J Med* 343(11): 808-810.

The Secretary of HHS, responding to serious criticism of the clinical research activities of the government and academic health centers proposed supporting a much strengthened oversight office with considerable powers. Oversight of research would be greatly enhanced.

Sieber, J. P., S; Rubin, Philip. (2002). "How (Not) to Regulate Social and Behavioral Research." *Professional Ethics Report* 15(2): 1-8.

The authors deal with apparent craziness on the part of IRBs, used to dealing with medical research, attributing harm to social science studies and delaying or stopping research proposals for what

seems to be ridiculous reasons. Good arguments; however, social scientists also are frequently oblivious of the harm they may do in their studies, for example, stigmatizing a group.

Siegler, M. (1998). "Ethical issues in innovative surgery: should we attempt a cadaveric hand transplantation in a human subject?" *Transplantation Proceedings* 30(6): 2779.

The author discusses the ethical and scientific validity of conducting the first cadaveric hand transplant. He applies criteria that Francis Moore has proposed years ago that includes good science, institutional probity, openness, and community discussion and decides that it is o.k. Since we have seen two face transplants by now, we can see that surgical innovation will continue apace.

Slater, E. E. (2005). "Today's FDA." *N Engl J Med* 352(3): 293-297.

The author, with considerable personal experience reviews the successes and deficiencies of the FDA. She recommends much strengthening post-marketing surveillance, getting proper leadership approved, improving the review process to more nearly match the strength of the pharmaceutical houses, and bringing down the costs of drugs by getting them generic sooner and transferring more agents to over-the-counter status. This is a very good article.

Steinbrook, R. (2004). "Peer Review and Federal Regulations." *N Engl J Med* 350(2): 103-104.

The author addresses the issue of peer review of information quality that the Federal government utilizes to make substantive policy decisions. The superficially good idea was questions as to the need that it fulfills in that the data seem to be good in the first place. Secondly, the selection of peer reviewers could politicize the process, especially if conflicted individuals were selected. Finally, some thought the whole idea was political, to get rid of troublesome findings. This is a very interesting discussion.

Woodward, B. (1999). "Challenges to Human Subject Protections in US Medical Research." *JAMA* 282(20): 1947-1952.

United States regulations governing federally supported research with human subjects derive in part from 2 international codes, the Nuremberg Code and the Declaration of Helsinki. The Declaration of Helsinki states that "concern for the interests of the subject must always prevail over the interests of science and society." The concept of minimal risk and the principle of informed consent are the key means by which US federal regulations seek to protect the rights and welfare of the individual in the research setting. Current trends in medical research--including increased funding, ever-greater capabilities of computers, development of new clinical tools that can also be used in research, and new research tools developed through research itself. These are creating greater demand for human subjects, for easier recruitment and conscription of these subjects, and for unimpeded access to patient medical records and human biological materials. Nationally and internationally, there are new pressures to subordinate the interests of the subject to those of science and society. This review is designed to sensitize the reader to the great difficulty of the task of protecting subjects in this environment.

(2004). *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection*. DHHS. Services, Federal Register. 69 (92): 26393-7.

This federal guideline asks IRBs and institutions to consider a variety of means to eliminate, document, disclose, and manage conflicts of interest. It is not overly prescriptive but it expects institutions to actively and effectively deal with conflicts of interest both of individual investigators and of IRB members. Conflict of interest committees distinct from IRBs are expected to be developed. Required reading for research administrators.

Shalowitz, D. I. and F. G. Miller (2005). "Disclosing Individual Results of Clinical Research: Implications of Respect for Participants." *JAMA* 294(6): 737-740.

This discussion piece should be read by everyone conducting research in which testing is done that may be of relevance to subjects. They claim that, in addition to informed consent, respect means that individuals have the right to learn about tests done on them as individual if they want the information. That obligation is not set down in any research rules as yet.

<http://jama.ama-assn.org/cgi/content/full/294/6/737>

Consents

Dye, L., S. Hendy, et al. (2004). "Capacity To Consent To Participate In Research -- A Recontextualization." British Journal of Learning Disabilities 32: 144-50.

In order to be able to carry out research in people with learning disabilities the issue of how to consent becomes important. The authors suggest that consent exist in a continuum involving both assessments of capacity, degree of risk, availability of surrogates and assent, etc, rather than a dichotomous decision for each individual.

Ross, L. F. (2004). "Children In Medical Research: Balancing Protection And Access--Has The Pendulum Swung Too Far?" Perspectives in Biology and Medicine 47(4): 519-36.

The author discusses the uncertain evolution of research in children from protection (paternalism) to access (autonomy) and the associated ethical dilemmas. It is largely a historical review.
http://muse.jhu.edu/journals/perspectives_in_biology_and_medicine/v047/47.4ross.html

Kovnick, J. A., P. S. Appelbaum, et al. (2003). "Competence to Consent to Research Among Long-Stay Inpatients With Chronic Schizophrenia." Psychiatr Serv 54(9): 1247-1252.

The authors did a study of the consenting capacity of a group of chronically hospitalized schizophrenics to see how many were competent and for what kind of research. While diminished competence was widespread some positive findings were demonstrable.
<http://ps.psychiatryonline.org/cgi/content/full/54/9/1247>

Nelson, R. and J. F. Merz (2002). "Voluntariness of consent for research: an empirical and conceptual review." Med Care 40(9): V69-V80.

These authors discuss the concepts surrounding voluntariness in voluntary informed consent. They elaborate on the vulnerabilities of potential research subjects and proceed with the ways in which investigations can influence participation to the extent of coercion. These are evaluated as ethical conclusions in research.

Bosk, C. (2002). "Obtaining voluntary consent for research in desperately ill patients." Med Care 40(9): V64-V68.

The author, in reflecting on the consent process for very seriously ill subjects, stresses the battle between hope (the therapeutic misconception) and reason (reading all the negative information provided). If we insist that reason prevails and the distinction between care and research be clear then some changes need to be made in the process of obtaining consent.

Kim S Y Hcaine , E D, et al. (2001). "Assessing the Competence of Persons with Alzheimer's Disease in Providing Informed Consent for Participation in Research." Am J Psychiatry 158(5): 712-717.

This study used the MacArthur Competence Assessment Tool--Clinical Research Version to examine the consenting capability of 37 subjects with mild to moderate Alzheimer's disease in comparison to controls. They found 62% of the subjects to be incompetent by not exceeding the cutoff score on at least one domain. The validity of this way of determining competency was subject to discussion.

Kuczewski, M. and P. Mashall (2002). "The decision dynamics of clinical research: the context and process of informed consent." Med Care 40(9): V-45-V54.

This very perceptive article elaborates on the informed consent process. They indicate that research on informed consent have concentrated on the form rather than dealing with recruitment that condition people about volunteering, the social and demographic characteristics of the potential volunteers, and the role of the primary care physician.

Nelson K, G. R., Brown J, Mangione CM, Louis TA, Keeler E, Cretin S (2002). "Do patient consent procedures affect participation rates in health services research?" Med Care 40(4): 283-88.

These authors report on an experiment forced upon them when 7 of 15 IRBs required pre-permission to send a questionnaire to subjects in a health services research investigation. Pre-permission substantially reduced acceptance. They would prefer no advanced permissions but would accept an "opt out" solution.

Daugherty, C. K. (1999). "Impact of Therapeutic Research on Informed Consent and the Ethics of Clinical Trials: A Medical Oncology Perspective." *J Clin Oncol* 17(5): 1601-.

The author provides a thoughtful historical review of "informed consent" with emphasis on oncology studies. He finds great weakness in the process, in the written consent and in the involvement of the physicians. This is an important article to review as it provides an excellent historical review of studies of the consent process as well as his analysis.

<http://www.jco.org/cgi/content/full/17/5/1601>

Corbie-Smith, G., S. B. Thomas, et al. (1999). "Attitudes and Beliefs of African Americans Toward Participation in Medical Research." *Journal of General Internal Medicine* 14(9): 537-546.

This focus group study of African Americans in 1997 demonstrated mistrust of scientists, doctors, and government. The participants reported feelings of exploitation of poor or minority patients. Even though they didn't understand it they knew that Tuskegee was wrong. They understand informed consent as giving up their autonomy. They did support the need for research in minorities.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1525-1497.1999.07048.x>

Eriksson, S. and G. Helgesson (2005). "Keep people informed or leave them alone? A suggested tool for identifying research participants who rightly want only limited information." *J Med Ethics* 31(11): 674-678.

This paper notes that some research participants fail to understand the study in which they are enrolled because it is their choice while for others it is the lack of adequate information. They argue that the appropriate responses to each of these is different. They suggest confronting the issue by asking a few questions about the potential subjects' beliefs and attitudes.

<http://jme.bmjournals.com/cgi/content/full/31/11/674>

Agre, P., F. Campbell, et al. (2003). "Improving informed consent: the medium is not the message." *IRB* 25(5): S11-19.

The authors reviewed the literature for studies addressing the question of whether augmentation of standard consent forms with videos, computer software, or enforced written material has a positive impact in subjects understanding of the protocol and willingness to volunteer. They actually review the 8 studies found addressing the subject. Although they were relatively negative, the studies showed variable improvement -- depending!

Arnason, V. (2004). "Coding and Consent: Moral Challenges of the Database Project in Iceland." *Bioethics* 18(1): 27-49.

This paper reviews the Icelandic medical, genealogical, and genetic databases, their linkages, and the requirements for individual informed consents in relation to societal consents. The author recommends an individual written authorization rather than a standard consent and "pressured consent" in database research.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1467-8519.2004.00377.x>

Kegley, J. (2004). "Challenges to informed consent." *EMBO reports* 5(9): 832-6.

Genetic research and stem cell research have raised new questions about the sufficiency of informed consent based on individuals. This paper reviews a number of these questions but does not try to resolve them.

<http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=15470376>

Gill, D. (2003). "Guidelines for informed consent in biomedical research involving paediatric populations as research participants." *European Journal of Pediatrics* 162(7 - 8): 455.

This report of the Ethics Working Group of the Confederation of European Specialists in Paediatrics delineates their guidelines for informed consent involving children. It involves respect for the dignity of the child, safeguarding the best interests of the child, protecting the child from harm, and assuring and protecting the privacy and confidentiality of the child.

<http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s00431-003-1192-0>

Foex, B. A. (2001). "The problem of informed consent in emergency medicine research." Emerg Med J 18(3): 198-204.

This paper gives the ethical background and rationale for conducting research on emergency conditions without prior informed consent, citing mainly the importance to society.

<http://emj.bmjournals.com/cgi/content/abstract/18/3/198>

Godard, B., J. Schidtke, et al. (2003). "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective." European Journal of Human Genetics 11(Supplement 2): S88-122.

This paper contains the results of a European meeting on DNA banking and review of applicable documents from around the world. It then reviewed the various ethical issues and ended up proposing standardizing policies for both the public and private sectors.

<http://www.nature.com/ejhg/journal/v11/n2s/abs/5201114a.html>

May, T. (2004). "Social Restrictions on Informed Consent: Research ethics and medical decision making." HEC Forum 16(1): 38-44.

This philosophical paper deals with the question of the extent to which social and community considerations can and should play a role in the decision of an individual to participate in research. In many respects the IRB acts for the community but questions may arise that evade the IRB. In developing countries and in relation to minority populations, sensitivity to community morals, cultures, and cohesion is especially important.

Goodyear-Smith, F., B. Lobb, et al. (2002). "International variation in ethics committee requirements: comparisons across five Westernised nations." BMC Medical Ethics 3(1): 2.

<http://www.biomedcentral.com/1472-6939/3/2>

This study reviewed the IRB procedures employed in 5 countries that were jointly conducting a study about the believability of testimony regarding alleged child abuse. There were substantial differences and these were discussed.

Hofman, N. (2004). "Toward critical research ethics: transforming ethical conduct in qualitative health care research." Health Care for Women International 25(7): 647-62.

The author discusses the problems with the standard model of the ethical conduct of research when carrying out qualitative research on a vulnerable population, in this case female drug users conducting illicit sexual activity in the US. She draws the problem as a cognitive and emotional divide between relatively untrained middle class interviewers who focus on the science and impoverished underclass women who focus on their payment. Little is done to empower the participants or to explain their common ground in learning how to improve the participants' lives. Several useful suggestions for improving the situation are made.

Edwards, S. D. and M. J. McNamee (2005). "Ethical concerns regarding guidelines for the conduct of clinical research on children." J Med Ethics 31(6): 351-354.

<http://jme.bmjournals.com/cgi/content/full/31/6/351>

This focuses on the difference between the British and Declaration of Helsinki guidelines for research on children. They prefer the Helsinki guidelines because the subject can never be used as a means only but must also be an end in respect to the research.

Kahn, J. (2005). "Informed Consent in the Context of Communities." J. Nutr. 135(4): 918-920.

The author revisits the change of IRB (and Federal) attention from protecting individuals (autonomy) to assuring equitable access (justice) and how involving communities complicates the issue. A very important set of concepts is examined here.

<http://jn.nutrition.org/cgi/content/full/135/4/918>

Casarett, D. J., J. H. T. Karlawish, et al. (2003). "Identifying ambulatory cancer patients at risk of impaired capacity to consent to research." Journal of Pain and Symptom Management 26(1): 615.

Cancer patients might have a limited capacity to be research subjects, This study used a competency test and protocol scenarios and found that ability to consent was related not to the cancer but to cognitive impairment, education, and aging.

<http://www.sciencedirect.com/science/article/B6T8R-4902FRW-7/2/448760762fb5650227298073016d28db>

Scherer, D. G., J. L. Brody, et al. (2005). "Financial compensation to adolescents for participation in biomedical research: Adolescent and parent perspectives in seven studies." *The Journal of Pediatrics* 146(4): 552.

This empirical paper studies the implications of payment to the participants in pediatric asthma research using protocol scenarios. They concluded that financial compensation was not a major motivator. However, there were significant differences in estimates that raise interesting questions about coercion.

<http://www.sciencedirect.com/science/article/B6WKR-4FW7GVF-18/2/bb70ba4a07293ed2c2b920123b20a02e>

Ballard, H., L. Shook, et al. (2004). "Neonatal Research and the Validity of Informed Consent Obtained in the Perinatal Period." *J Perinatology* 24(7): 409-15.

This article evaluates the effectiveness of the informed consent process for a study in a NICU. They were somewhat concerned about both the knowledge of the procedures and the purpose on the part of the parents, especially the fathers. I believe, however, that they did as well as others. Some people really don't want to learn the details.

<http://www.nature.com/jp/journal/v24/n7/full/7211142a.html>

Regidor, E. (2004). "The Use Of Personal Data From Medical Records And Biological Materials: Ethical Perspectives And The Basis For Legal Restrictions In Health Research." *Social Science & Medicine* 59(9): 1975.

Personal medical information is essential when carrying out many kinds of human research. When clinical databases are mined in the US and elsewhere, the protocol must be extremely precise, the data extracted limited, and a waiver of informed consent obtained from an IRB. The author discusses the preconceptions utilized in passing these restrictive rules and indicates that they lack an effective logical rationale. Interesting reading, especially for those who have been hamstrung by HIPAA.

<http://www.sciencedirect.com/science/article/B6VBF-4C6KPJX-1/2/600dde50f50627ebcd25a4d402f8aab3>

Joffe, S. and J. Weeks (2002). "Views Of American Oncologists About The Purposes Of Clinical Trials." *J Natl Cancer Inst* 94(24): 1847-53.

This study raises serious questions about the preparation of oncologists for carrying out clinical trials. A large proportion of clinical oncologists believed that the purpose of the trial was to improve therapy for the individual participants rather than to produce generalizable knowledge about cancer treatment to advance future therapy. That is inconsistent with the principles of clinical research.

Roberts, L. W. (2002). "Informed Consent and the Capacity for Voluntarism." *Am J Psychiatry* 159(5): 705-712.

The author proposes considering four domains of influences on voluntariness that apply to everyone and must be considered in the determination of whether fully informed consent is possible: 1) Development factors; 2) illness-related considerations; 3) psychological issues and cultural/religious values; 4) External features and purposes. She discusses how these affect the informed consent process, especially in psychiatric patients.

Biros, M. H. (2003). "Research without consent: Current status, 2003." *Annals of Emergency Medicine* 42(4): 550.

A review of the status of the 1996 ruling by the NIH and FDA on the allowance of research in resuscitation and emergency medicine without prior informed consent. Very little research had been done under that rubric and the article reviews the reasons why and makes some suggestions.

Pucci E, B. N., Borsetti G, Rodriguez D, Signorino M. (2001). "Information and competency for consent to pharmacologic clinical trials in Alzheimer disease: an empirical analysis in patients and family caregivers." *Alzheimer Dis Assoc Discord* 15(3): 146-54.

The authors studied the competency to give informed consent was compared in Alzheimer's disease patients and their caregivers. The Mini-Mental State Examination was useful in determining competence. They request support on methods to enroll Alzheimer's patients.

Wendler, D. (2004). "Can We Ensure That All Research Subjects Give Valid Consent." *Arch Intern Med* 164: 2201-4.

This article raises the question of the degree to which study participants actually understand the consent form they are signing. It proposes post-decision questionnaires to improve understanding.

IRBs

(2003). "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research." *Journal of Clinical Oncology* 21(12): 1-10.

Cutcliffe, J. R. and P. Ramcharan (2002). "Leveling the Playing Field? Exploring the Merits of the Ethics-as-Process Approach for Judging Qualitative Research Proposals." *Qual Health Res* 12(7): 1000-1010.

Qualitative research involving in depth interviews is associated with a continuing interaction of interviewer and interviewee, an ability of the interviewer to subtly or not so subtly coerce (see the movie, Capote) and for the subject to feel locked in to continue. IRBs have no, they say, been kind to qualitative research. They discuss the concepts of implementation of "consent as a process."

<http://qhr.sagepub.com/cgi/reprint/12/7/1000>

Whittle, A., S. Shah, et al. (2004). "Institutional Review Board Practices Regarding Assent in Pediatric Research." *Pediatrics* 113(6): 1747-1752.

This telephone survey of IRB chairpersons queried about the process of assent. They found great variability in the presence of criteria (age cutoff). They also varied on payment to the children and/or to the parents. It may have had some influence in getting IRBs to more effectively defer their rules for research with children.

<http://pediatrics.aappublications.org/cgi/content/full/113/6/1747>

Motil, K., J. Allen, et al. (2004). "When a research subject calls with a complaint, what will the IRB do?" *IRB Ethics and Human Research* 26(1): 9-13.

The authors describe the process by which the Baylor College of Medicine IRB deals with research subject complaints. It is based on a carefully orchestrated inquiry mechanism that is designed to get objective information and result in justice.

Edwards, S. J. L., R. Ashcroft, et al. (2004). "Research Ethics Committees: Differences and Moral Judgement." *Bioethics* 18(5): 408-427.

This paper deals with the inconsistencies between research ethics committees and includes that it is inappropriate to try to make them all behave identically. They argue that different committees may have different ideas of justice, that there is no single moral standard for such committees, and third that committees have different processes. TO this I add that calculation of risk and benefit is not an exact science.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1467-8519.2004.00407.x>

Coffey, M. J. and L. Ross (2004). "Human Subject Protections in Genetic Research." *Genetic Testing* 8(2): 209-213.

This paper considers the Certificate of Confidentiality, a tool available to researchers to keep personal health-related informed from those who might seek primary data from a study. They also reflect on how after documentation of other protective instruments is missing from research reports.

<http://www.liebertonline.com/doi/abs/10.1089/gte.2004.8.209>

Ray, W. A. and C. M. Stein (2006). "Reform of Drug Regulation -- Beyond an Independent Drug-Safety Board." *N Engl J Med* 354(2): 194-201.

<http://content.nejm.org/cgi/content/extract/354/2/194>

This paper thoroughly reviews the weakness of our drug regulation system and suggests adding new and expansive elements to it. The foci are on complete information before and after a trial and processes to monitor drugs past release even to the point of requiring additional studies. What's ironic to me is that if both sponsors and the FDA were more honest and effective in the first place, their horrible examples could have been prevented.

Hearnshaw, H. (2004). "Comparison of requirements of research ethics committees in 11 European countries for a non-invasive interventional study." *BMJ* 328(7432): 140-141.

<http://bmj.bmjjournals.com/cgi/content/full/328/7432/140>

This brief study demonstrates the different ways IRBs in various countries handle a protocol. The author suggests that much of the effort is time consuming and does nothing to help research participants.

Califf, R. M., M. A. Morse, et al. (2003). "Toward protecting the safety of participants in clinical trials." *Controlled Clinical Trials* 24(3): 256.

<http://www.sciencedirect.com/science/article/B6T5R-48KCM54-2/2/72c360ccf7d1b393918aa883c7bd428c>

This excellent paper reviews clinical research and analyzes the weaknesses in monitoring. Safety data are particularly problematic. They recommend strengthening data and safety monitoring boards, teaching investigators good clinical practices, more local scrutiny of single site studies, and careful oversight of multi-center studies.

Burman, W., P. Breese, et al. (2003). "The effects of local review on informed consent documents from a multi-center clinical trials consortium." *Controlled Clinical Trials* 24(3): 245.

This interesting review of sending an approved centralized research protocol for local review resulted in many changes -- median 46/5 that added complexity but did not improve meaning. It took an average of 104 days to accomplish this. IRBs should read this article and take heed.

Dickenson, D. and J. Ferguson (2005). "Advisory Document for Retained Organs Commission." University of Birmingham, UK: Centre for Global Ethics.

This document addresses the burning issue of retained organs and the rights of donors. They suggest a modified property rights approach to regulation of the practice.

http://www.globlethics.bham.ac.uk/consultancy/Retained_organ.htm

Miller, F. G. (2002). "Ethical Significance of Ethics-Related Empirical Research." *J Natl Cancer Inst* 94(24): 1821-1822.

This editorial comments on an empirical study of oncologists' understanding of trials in which they participate. The author supports the idea of empirical ethics research and points out that it too can be excellent on trivial, well or poorly done.

<http://jncicancerspectrum.oxfordjournals.org/cgi/content/full/jnci;94/24/1821>

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.

Churchill, L., D. Nelson, et al. (2003). "Assessing Benefits in Clinical Research." *IRB Ethics and Human Research* 25(3): 1-8.

These authors did an empirical study of what benefits were assessed by 43 IRBs by doing a taped standardized interview with a senior member or chair. The tapes were transcribed, anonymized, and analyzed. The results show considerable variability in approaches to determining potential benefits to research subjects.

Levine, C., R. Faden, et al. (2004). "'Special Scrutiny': A Targeted Form of Research Protocol Review." *Ann Intern Med* 140(3): 220-223.

This interesting paper proposes that clinical research protocols with increased risk, especially with low benefit, studies of really novel compounds, and research with a somewhat questionable design should receive "special scrutiny" from the IRB. It's disappointing that they never mention DSMBs whose function is to examine research as it progresses nor the RSA program of GCRCs.

Shah, S., A. Whittle, et al. (2004). "How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?" JAMA 291(4): 476-482.

Federal regulations allow children to be enrolled in clinical research only when IRB determines that the risks are minimal or a minor increase over minimal, or that the research offers a prospect of direct benefit. This study was designed to learn how IRBs actually determine risk vs benefit and to see whether they are consistent. They did a telephonic survey of IRB chairs and asked them 21 questions. They found that the only thing they generally agreed was minimally risky was a blood draw. They had a remarkably jaundiced eye toward what one would normally think as low risk interventions. They thought very little of payment as a benefit, but did accept psychological benefit. There was great variance among IRBs. They suggest some guidelines about risk be applied broadly. This is an excellent experimental paper.

Slater, E. E. (2002). "IRB Reform." N Engl J Med 346(18): 1402-1404.

An editorial detailing aspects of IRB reform that included a pilot NCI project on a single review of multicentric studies with local element reviewed locally.

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.

Equipoise

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

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

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 E ₄)	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, be 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 overall for the research participants.

Company representatives agreed wholeheartedly 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-](http://www.nature.com/nm/journal/v10/n6/abs/nm0604-570.html)

[570.html;jsessionid=00E29673439DE2E30C826750460B6D20](http://www.nature.com/nm/journal/v10/n6/abs/nm0604-570.html)

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 no 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/ea1fedba809650b94c8231b368ecded>

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.

Itlis, 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." Hastings 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). "Equipoise 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 equipoise 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.

Chapter 4: CONFLICTS OF INTEREST (COI)

A. Definitions

Interest

An interest may be defined as a commitment, goal, or value held by an individual or an institution.

Examples include a research project to be completed, gaining status through promotion or recognition, and protecting the environment. Interests are pursued in the setting of social interactions.

Conflict of Interest (COI)

A conflict of interest exists when two or more contradictory interests relate to an activity by an individual or an institution. The conflict lies in the situation, not in any behavior or lack of behavior of the individual. That means that a conflict of interest is not intrinsically a bad thing.

Examples include a conflict between financial gain and meticulous completion and reporting of a research study or between responsibilities as an investigator and as a treating physician for the same trial participant.

Institutional examples include the unbalancing of the institutional mission by acceding to the space requests of a large donor for an idiosyncratic program.

Other definitions include:

Conflicts of interest are “situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator’s judgement in conducting or reporting research.” AAMC, 1990

“A conflict of interest in research exists when the individual has interests in the outcome of the research that may lead to a personal advantage and that might therefore, in actuality or appearance compromise the integrity of the research.” NAS, Integrity in Scientific Research

B. Consequences of a COI

When an individual COI exists, then independent of the behavior of the investigator, those knowledgeable about the study must take the COI into account when judging the validity of the study.

Beyond that, in clinical research, the well being of the subjects may also be compromised by a COI and this has become an overarching factor in the

regulation of financial COIs in clinical research. As noted above, the well being of the participants is paramount and trumps the completion of the research.

C. Government intervention

The Bayh-Dole act of 1980 made it possible for institutions and individuals to recover substantial financial rewards for their intellectual property as royalties and as equity. Furthermore, the reliance of research sponsors on the expertise of faculty to support a trial agent encouraged substantial payments to accrue to faculty as consultants, often on a continuing basis. Optimizing these financial interests produces a COI situation in relation both to the conduct of the research and to the welfare of trial subjects.

Responding to these realities, the NIH, FDA and individual institutions developed rules for investigators to limit the impact of investigator COIs under Federal rules. A reminder follows

<http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-05-013.html>

The actual rules can be found at this URL

<http://grants.nih.gov/grants/guide/notice-files/not95-179.html>

The key provisions are, redacted:

“Investigators are required to disclose to an official(s) designated by the institution a listing of Significant Financial Interests (and those of his/her spouse and dependent children) that would reasonably appear to be affected by the research proposed for funding by the PHS. The institutional official(s) will review those disclosures and determine whether any of the reported financial interests could directly and significantly affect the design, conduct, or reporting of the research and, if so, the institution must, prior to any expenditure of awarded funds, report the existence of such conflicting interests to the PHS Awarding Component and act to protect PHS-funded research from bias due to the conflict of interest.

The definition of "Significant Financial Interest" in 50.603 has been changed in several respects. The exception for financial interests in business enterprises includes salary, royalties or other payments not reasonably expected to exceed \$10,000 per annum. Alternative measures of \$10,000 in value include stock or no more than five percent ownership interest.”

In my view, \$10,000 or an ownership position even if it has no cash value constitutes a significant COI and should be at least disclosed. Disclosure requirements are very poor in that the statute limits them to the institutional administrators and the COI committee. They should be required to disclose every time they present or publish research.

D. Industry Sponsorship

Studies of industry sponsorship reveal profound influence over study design, analysis and interpretation of data (bias). They also engage in suppression of results (negative, AEs). They promulgate secrecy among researchers by negotiating confidentiality clauses in contracts.

Sometimes results are made public while bypassing the peer review system.

“Drug company money and investigator COIs have so corrupted clinical trials research that drug companies control what clinicians and patients know and don’t know about the \$200,000,000 worth of drugs and devices they are consuming.”

“This is all about bypassing science. Medicine is becoming a sort of Cloud Cuckoo Land, where doctors don’t know what papers they can trust in the journals.” Drummond Rennie of JAMA

E. Professional Societies

Professional societies take huge amounts of pharmaceutical money to support their annual meetings and other activities. The funding may unbalance the science presented at the meeting. They permit highly biased Continuing Medical Education segments.

Professional societies do not carefully control the listing of COIs in the scientific presentations. They foster over-the-top media presentations of advances. They permit biased articles and supplements in their journals.

F. Clinical Practice Guidelines

The practice of “evidence based medicine” has led to the development of guideline for the treatment for many medical conditions, based on meetings of “experts, ” often from professional societies. Treatment guidelines generally support the use of more procedures and medications. It was recently shown that

33% of guideline authors have financial interests in the drug

50% guidelines had no COI documentation

34% of guidelines stated no COIs

50% had at least one author receiving research support

43% had at least one author who had been a paid speaker for the company

Derived from National Guideline Database

Nature, Oct 20,2005

G. Other initiatives

The people who need to know about the COI are those who learn about the results of a study and have to interpret it.

The decision about disclosure of a COI should never be left to the possessors of the COI because they are susceptible to self-deception or worse about the influence of the COI on their research behavior.

Thus, NIH and other funding agencies, Professional Societies sponsoring research meetings, and the leading journals now require disclosure of COIs as a precondition for reviewing, editing, presenting and publishing research and research proposals but there is no means of enforcing the requirement. Voluntary revelation of a COI precludes the reviewing, of a grant or paper. A COI must be disclosed in presenting science.

The Appearance of a COI must be avoided or disclosed. Consider the NY Times test. "Would you want the relationship published in the NY Times?" The presence of Conflicts of Interest tends to diminish the credibility of a study.

The most common conflicts of interest in research are between financial or career rewards and the integrity of a research study, report, presentation, or review.

It's necessary to manage outside income,
 for consultations
 for lectures,
 for courses,
 for research
when conducting a clinical trial.

Full disclosure of conflicts of interest should be required in consent forms, papers, lectures and presentations. COIs may result in:

1. Loss of objectivity
2. Reordering of priorities towards applied research
3. Degradation of the *nature of science* as an open and collegial enterprise
4. Exploitation of trainees
5. Transfer of time and interest to Commercial ventures

H. COIs in Financial Consulting

A new kind of COI has just come to light as the practice has become much more widespread through investigative reporting of the Seattle Times. Many investigators are recruited to consult for financial entities including venture capital firms, hedge funds and investment houses to inform them of the latest developments in their field. The pay is good and the investigators feel quite

flattered. Sometimes, the investigators have provided privileged information about an ongoing clinical trial about which both they and their institutions signed confidentiality statements. In all instances, the goal of the consulting groups is to learn information of investment value before the competition. After the initial concern, apparently this area of concern has lost immediacy.

Cases: Chapter 4

Case: Remembra

Dr. Zhivago, in NIH supported research, made remarkable progress in memory studies by identifying a new receptor “C” responsible for instilling and preserving memories. In mice and rats substantial improvements in memory were produced in a short time as demonstrated by performance studies. Activating C in monkeys permitted substantial acceleration in achieving cognitive skills and great enhancement in cognitive capability. Zhivago approached her institution’s Office of Technology to arrange for patent and licensing.

The University had just established a research incubator to carry its inventions to a more advanced stage so that it would be able to retain a greater portion of the financial benefits to come from the products of discovery.

The Office of Technology suggested that Zhivago establish a company with the university to exploit her discovery and develop small molecule receptor agonists for use in treating certain forms of mental retardation as well as Alzheimer’s and other disorders. Neither Zhivago, nor the university officials were unaware of the fact that once approved, the agonists would most likely be taken by normal persons to augment their intellectual capabilities.

Zhivago was told that the university would advance up to 1 million dollars of its endowment on this company and that as funding requirements grew, depending on the situation, either more new funds would be allocated or venture capitalists would be invited to invest.

Zhivago, figuring that if she reduced her clinical burden and got out of teaching, which were easily arranged, she could spare 30% of time for this project and suggested to her senior technician Anna Karenina that she take a job at the new company, LEARN, with a significant salary increase, and manage the practical details of creating C-receptor agonists under Zhivago’s direction. When the time came, Zhivago would test her drug first in mentally retarded children, her specialty.

Dr. Zhivago delayed publication of her discovery for four months in order to accomplish the patent and license work.

Upon learning of the discovery, a couple of very large drug companies with an interest in mental health volunteered financial support for priority in the bidding for the new agent when it was developed.

The entire university leadership was highly attuned to this activity as the result of their big stake in the outcome.

Zhivago found that it was very difficult to recruit someone as effective as Anna to run her lab where she was expected to continue to perform at a high intellectual level.

Zhivago found that she needed a lot of assistance with designing, synthesizing and testing CR agonists. Pharmacologists from the university were asked to help and they asked for equity in return. The Pharmacologists were knowledgeable but unwilling to commit enough time to oversee the effort.

Three and one half million dollars and two years later, a potent CR agonist was available for testing. It was called Remembra.

The IRB, with an inquiry from the university President urging expediency, approved the Phase I and II trials. In a total of 25 subjects the pharmacokinetics and acute toxicity studies were completed satisfactorily.

As Dr. Zhivago gears up for the clinical test of Remembra, she learns that her NIH renewal was not going to make the grade because of poor recent productivity. She thinks, "If this works, I won't need to keep applying for grants."

While the IRB was initially reluctant to approve Dr. Zhivago's role in both managing and carrying out the Phase III placebo controlled double blinded trial, with a little institutional encouragement the protocol was approved and Zhivago began testing Remembra on mentally retarded adolescents who required special schooling. Even though the study was double-blinded, the progress on Remembra was so dramatic that everyone thought they knew who was taking the real drug. Treated students were able to learn and retain much more rapidly than ever before.

Enthusiasm at the school got out and reached university administration, which reveled in the possibility that one of their investments might pay off.

About 3 months into the six-month trial it was noted that some of the participants began to have episodes of sweating and confusion that came and went. The teachers and investigators reported these events and when the Data and Safety monitoring Board was informed, one of the investigators suggested measuring the blood sugar during episodes and sure enough, the symptoms were found to be due to hypoglycemia (very low blood sugar).

Since there were no severe episodes and the episodes were treatable with orange juice, the DSMB suggested providing frequent meals and teaching the families and teachers of the students how to treat hypoglycemia. The IRB required an amendment to both the protocol and the consent form recognizing the adverse event.

By the fifth month the adolescents were gaining a lot of weight and on one occasion a participant went into hypoglycemic coma and had to be treated in the E.R.

The DSMB decided to stop the trial for safety reasons even though the participants on Remembra were learning at an impressive rate and the teachers wanted it continued. The DSMB heard an appeal from the university president for the sake of the mentally retarded to continue the study but they did not budge.

One of the teachers told the story of Remembra to the N.Y. Times, which published a long article on the story. Shortly thereafter Dr. Zhivago received a call from a major drug company about the possibility of developing Remembra as a treatment for diabetes.

1. What conflicts of interest exist in this scenario?
2. Remembra has potential. How can the ethical issues surrounding its testing be resolved?
3. How does the idea of improving on human intelligence strike you ethically?
4. If you were the CEO of LEARN what actions would you take now?

Case: Conflict of Interest Committee

You are a member of your institution's conflict of interest committee charged with the responsibility of determining the significance of Eric Jensen's conflicts of interest (COI) and to manage it. You are the primary reviewer for Jensen's proposal. He has invented an electrical device that markedly accelerates the fracture-healing rate. This was brought to the intellectual property office where a patent was requested. Jensen also formed a company to exploit the patent with the University. They induced a large medical apparatus company to manufacture and market the device. The university and Jensen's company would receive equity and royalties.

Jensen receives a prototype of the commercial version of the device and decides to conduct a clinical trial on healing rates comparing the device with conventional treatment. He will carry out a blinded study using the device appropriately or in an inactive mode.

1. Please comment on the proposed arrangement as primary reviewer for the COI committee.
2. What are the limits on a faculty member's interest in his/her company's ownership and function?
3. What does "conflict of commitment mean in this setting."

Case: Expert consultant

Going through your E-mails you find the following:

Hansen and Question, a commercial analysis company, is conducting in depth 30 minute interviews with thought leaders in your field about dilational cardiomyopathy for which a new molecular mechanism was just uncovered.

The E-mail indicates that they have been commissioned by a pharmaceutical company to get a further understanding of approaches to the management of this condition. They are willing to pay you \$500 for a 30 minute, one on one interview. The E-mail indicates that all your opinions will be reported anonymously in the final report.

As an expert on cardiomyopathy with definite views, you feel that might have a lot to offer the company; after all, you are the PI on a sophisticated study of cardiomyopathy at this very moment.

- 1) Should you respond to the E-mail?
- 2) What questions should you ask if you chose to respond?
- 3) Are there any constraints in relation to giving your opinion?
- 4) What is the university's involvement in this kind of activity and what should it be?

Chapter 4 Bibliography

Cohen, J. J. (2001). "Trust Us to Make a Difference: Ensuring Public Confidence in the Integrity of Clinical Research." *Acad Med* 76(2): 209-214.

Investigators' and institutions' financial conflicts of interest in clinical research raise serious questions about the objectivity of such research, the safety of human subjects, and the threat to public trust in the integrity of clinical research. Yet the author makes clear that a conflict of interest is a state of affairs, not a behavior, and therefore not automatically a manifestation of improper actions. But it is clear that both non-financial conflicts of interest and financial ones are double-edged: they can motivate individuals to do their best work but also can compromise judgment and undermine objectivity. The author offers eight suggestions for what academic medicine's leaders might do in this regard (comply with existing full-disclosure requirements; establish principles governing institutional conflicts of interest; etc.). He closes by reiterating that the pursuit of clinical research depends entirely on the ability and willingness of the research community to merit public trust.

(2003). "Protecting Subjects, Preserving Trust, Promoting Progress I: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research." *Acad Med* 78(2): 225-236.

(From the Executive Summary) In December 2001, the AAMC Task Force on Financial Conflicts of Interest in Clinical Research released this report, the first of two (both published in this issue of *Academic Medicine*). This report focuses on gaps in existing federal financial disclosure regulations of individual conflicts of interests, finding that additional scrutiny is recommended in two areas: human subjects research and privately sponsored research. The task force suggests that when potential conflicts exist, a conflicts of interest committee should apply a rebuttable presumption against engaging in human subjects research. The task force recommends that the circumstances giving rise to the presumption against the proposed activity be balanced against compelling circumstances in favor of the conduct of the research. The AAMC task force delineates core principles to guide institutional policy development. First, an institution should regard all significant financial interests in human subjects research as requiring close scrutiny. Second, in the event of compelling circumstances, an individual holding a significant financial interest may be permitted to conduct the research. Whether circumstances are deemed compelling will depend in each case upon the nature of the science, the nature of the interest, how closely the interest is related to the research, and the degree to which the interest may be affected by the research. Four other core principles for development of institutional policies are identified in the report, pertaining to reporting, monitoring, management of conflicts, and accountability.

(2003). "Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research." *Acad Med* 78(2): 237-245.

(From the Executive Summary) The AAMC Task Force on Financial Conflicts of Interest in Clinical Research issued this report, the second of two, in October 2002. (The first report is also published in this issue of *Academic Medicine*.) This report offers a unique perspective on the new phenomenon of "institutional" conflicts of interest. The task force acknowledges the diverse obligations of academic institutions that conduct research and also invest in--and accept the philanthropy of--commercial research sponsors. The task force emphasizes the importance of disclosing institutional financial interests as an integral part of the research process, critical to allaying public concerns, and to strengthening the trust relationship between research subjects, the public and the scientific community. The task force found that the safety and welfare of research subjects and the objectivity of the research could be--or could appear to be--compromised whenever an institution holds a significant financial interest that may be affected by the outcome of the research. Thus, the task force recommends separating the functional and administrative responsibilities related to human subjects research from those related to investment managing and

technology licensing, and encourages the establishment of institutional conflicts-of-interest committees. As in the first report, the task force recommends that institutions should develop policies establishing a rebuttable presumption against the conduct of research at or under the auspices of an institution where potential conflicts in human subjects research are identified. This presumption against engaging in the research is to be balanced against compelling circumstances in favor of the conduct of the proposed research activity.

Kelch, R. (2002). "Maintaining the public trust in clinical research." *N Engl J Med* 346(4): 285-7.
This is a laudatory commentary on the AAMCs report on individual conflicts of interest.

(2003). Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. *Federal Register*. 68: 15456-15460.

The Office of Public Health and Science (OPHS), Department of Health and Human Services (HHS) announces a final guidance document for Institutional Review Boards (IRBs), investigators, research institutions, and other interested parties, entitled Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. This guidance document raises points to consider in determining whether specific financial interests in research could affect the rights and welfare of human subjects, and if so, what actions could be considered to protect those subjects. This guidance applies to human subjects research conducted or supported by HHS or regulated by the Food and Drug Administration.

Angell, M. (2000). "Is Academic Medicine for Sale?" *N Engl J Med* 342(20): 1516-1518.

This position paper uses evidence mostly from publications to argue that conflicts of interest are so pervasive so as to compromise the integrity of much medical publication.

Bekelman, J. E., Y. Li, et al. (2003). "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review." *JAMA* 289(4): 454-465.

This was a meta-analysis of the quantitative analytic literature on conflicts of interest in biomedical research from 1980 to 2002 using a variety of search techniques for materials. In 34 studies meeting all their criteria they show that about ¼ of the investigators had industry affiliations and 2/3 of academic institutions hold equity in start-ups that sponsor research. They claimed a relationship between industry sponsorship and positive conclusions. Industry sponsorship was also associated with restrictions on publication and data sharing. They concluded that conflicts of interest can have a powerful effect on biomedical research reports.

Bentley, J. P. and P. G. Thacker (2004). "The influence of risk and monetary payment on the research participation decision making process." *J Med Ethics* 30(3): 293-298.

This study used pharmacy students' reactions to scenarios varied by risk and payment to determine the extent to which they affected decisions to participate in a clinical trial. They found that money did help enlist subjects but they were not blinded to the risks.

Blumenthal, D. (2003). "Academic-Industrial Relationships in the Life Sciences." *N Engl J Med* 349(25): 2452-2459.

The author describes the evolving set of relationships between academic institutions and industry as it pertains to biological developments. He points out the rapid progress of biotechnology and the significant support of research by industry. He also points out the influences on scientific integrity and diminished quality of treatment of research subjects. A very important paper.

Blumenthal, D. (2004). "Doctors and Drug Companies." *N Engl J Med* 351(18): 1885-1890.

The author describes the evolving nature of the relationships between doctors and drug companies over the 20th century and the influences that the companies have come to exert over medical practice and research. He also discusses efforts to manage these relationships. Conflicts of interest pervade. This is a very powerful statement and uncomfortable reading for physicians.

Blumenthal, D., N. Causino, et al. (1996). "Relationships between Academic Institutions and Industry in the Life Sciences -- An Industry Survey." *N Engl J Med* 334(6): 368-374.

Despite growing acceptance of relationships between academia and industry in the life sciences, systematic, up-to-date information about their extent and the consequences for the parties involved remains scarce. They surveyed a representative sample of life-science companies in the United States to determine their relationships with academic institutions by telephone from senior executives of 210 life-science companies (69%). Ninety percent of the companies had relationships with an academic institution in 1994. Fifty-nine percent supported research, providing approximately 11.7 percent of their research-and-development funding. Over 60 percent of those companies had received patents, products, and sales as a result. The companies also reported that they often had agreements to keep the results of research secret beyond the time needed to file a patent. These relationships need greater scrutiny.

Bodenheimer, T. (2000). "Uneasy Alliance -- Clinical Investigators and the Pharmaceutical Industry." *N Engl J Med* 342(20): 1539-1544.

The author details the uncomfortable relationship between clinical investigators who carry out research on new drugs and industry that has a powerful vested interest in the success of their products. Conflicts of interest are widespread with adverse consequences for the science.

Boyd, E. A. and L. A. Bero (2000). "Assessing Faculty Financial Relationships With Industry: A Case Study." *JAMA* 284(17): 2209-2214.

The authors reviewed disclosure forms at UCSF to determine more about clinical and basic science faculty relationships with industry. By 1999, almost 7.6% of faculty investigators reported personal financial ties with sponsors of their research, including paid speaking engagements 34%. 33% had consulting agreements, and 32% involved the investigator holding a position on a scientific advisory board or board of directors. 14% involved equity ownership, and 12% involved multiple relationships. The advisory panel recommended managing perceived conflicts of interest in 26% of the cases. They considered this to be a growing problem that required management.

Boyd, E. A., M. K. Cho, et al. (2003). "Financial Conflict-of-Interest Policies in Clinical Research: Issues for Clinical Investigators." *Acad Med* 78(8): 769-774.

They questioned faculty at UCSF and Stanford who conducted clinical research about their knowledge of and attitudes towards conflict of interest policies. The campus COI policies were a mystery to more than half of those interviewed. Many investigators felt that, rather than the university, monitoring COIs was the job of professional societies, (who have no clout) the public (that understands nothing about this) and, individual investigators (who routinely engage in self-deception) should monitor conflicts of interest. Administrators and policymakers have to find a way to convince investigators, both clinical and nonclinical, of the serious problems of bias and co-optation associated with financial relationships with industry.

Brainard, J. (2001). Federal Rules on Conflicts of Interest in Biomedical Research Are Inadequate, GAO Finds. *The Chronicle of Higher Education*. Washington.

The GAO pointed out what everyone knew and was glad of, namely that COI regulations were weak and unenforceable.

Bramstedt, K. (2003). "Research subject advocates: to whom are they loyal?" *Clin Invest Med* 26(2): 64-9.

The author deals with the issue of conflicts of interest in the activities of Research Subject Advocates. This is based largely on who is paying them. Of course, the main issue is what are they paying them for. GCRC RSAs, for example are paid to support the subjects and they should normally operate in that manner. She deals with the Abiomed artificial heart case in which the subject advocate was sued as wrongly representing the institution. How hard is it for subjects to get the kind of support they need in difficult studies with considerable risk?

Brownlee, S. (2004). Doctors Without Borders: Why you can't trust medical journals anymore. *Washington Monthly*.

This reporter discusses the Nemaroff case in which a physician wrote a review article for *Nature Neuroscience* in which he failed to reveal his many and profitable conflicts of interest in recommending

drug treatments for psychiatric illness. She goes on to discuss in vivid terms the insidious downside of these conflicts and the great efforts made by industry to involve prominent physicians in supporting their drugs.

Calfee, J. E. (2001). "Pharmaceutical Price Controls and Patient Welfare." *Ann Intern Med* 134(11): 1060-1064.

He argues forcefully against price controls for drugs as inhibiting innovation and eliminating the risk capital necessary to bring new ideas to market by killing incentive.

Campbell, E. G., J. S. Weissman, et al. (2001). "Market Competition and Patient-oriented Research: The Results of a National Survey of Medical School Faculty." *Acad Med* 76(11): 1119-1126.

They tried to determine the impact of carrying out clinical care in a competitive environment on research productivity by surveying research faculty (2336 responses). They found that both basic and clinical research productivity was adversely affected by the need to do more clinical care in the most competitive markets. Good study demonstrating the impact of changing priorities for survival.

Cech, T. and J. Leonard (2001). "Science and business. Conflicts of interest--moving beyond disclosure." *Science* 291(5506): 989.

As director of the Howard Hughes Institute the author makes his point about conflicts of interest in research and indicates a strong position in avoiding them.

Cho, M., R. Shohara, et al. (2000). "Policies on faculty conflicts of interest at US universities." *JAMA* 284(17): 2203-8.

This excellent study has become somewhat dated because of the impacts of studies and changing policies secondary to various forces acting on universities. It reviewed COI policies of 89/100 polled Institutions. They found that there was great variability in types of relationships that were controlled, the financial limits, and the disclosures required. They recommended much more specific and consistent rules throughout the country.

Coyle, S. L. (2002). "Physician-Industry Relations. Part 1: Individual Physicians." *Ann Intern Med* 136(5): 396-402.

This is part 1 of a 2-part paper on ethics in physician-industry relationships. Part 1 offers advice to individual physicians; gives recommendations to medical education providers and medical professional societies. While physicians and commerce share an interest in advancing medical knowledge they diverge in that the former is a fiduciary for the patient and the latter has responsibility primarily toward its investors. This can lead to conflicts of interest, biased reporting and issues with appropriate experimental design. While physicians and trainees think they are impervious to Drug Company blandishments, the companies know better. So physicians have to decide for themselves what gifts raise no problems and which do. A general guideline is inexpensive and no strings attached. But, in our society, the very act of accepting a gift creates an obligation. Other financial ties between physicians and industry include honorariums for speaking or writing and payment for doing clinical research. These also can influence a physician's beliefs and practices. The paper goes into considerable detail.

Coyle, S. L. (2002). "Physician-Industry Relations. Part 2: Organizational Issues." *Ann Intern Med* 136(5): 403-406.

This is part 2 of a 2-part paper on ethics and physician-industry relationships. Part 1 offers advice to individual physicians; part 2 considers medical education providers and medical professional societies. While industry develops advances in medicine it also plays a key role in disseminating up-to-date medical information. The problem is bias and providers of the education must protect against that bias by presenting objective and balanced information. To do that, they must be careful of conditions under which money is collected to carry out their programs. They should insist on control of the content and conditions of the learning process. Disclosure of industry sponsorship to students, faculty, and continuing medical education trainees is mandatory. This also applies to medical societies.

Dana, J and G. Lowenstein (2003). "A social science perspective on gifts to physicians from industry." *JAMA* 290(2): 252-5.

The article uses behavioral science to examine the nature of conflicts of interest. It examines the "self-service bias" in our perceptions of fairness, indicating an individual's notion of fairness is inherently biased toward his/her own self-interest. This makes the article very good in uniting cross-arguments into one inherent principle: human nature.

DeAngelis, C., P. Fontanarosa, et al. (2001). "Reporting financial conflicts of interest and relationships between investigators and research sponsors." *JAMA* 286(1): 89-91.

JAMA was one of the first journals to insist on disclosure of COIs in all papers, editorials, etc coming out of their shop.

Drazen, J. M. and G. D. Curfman (2002). "Financial Associations of Authors." *N Engl J Med* 346(24): 1901-1902.

Having come upon scathing criticism for publishing review articles written by persons with substantial conflicts of interest without identifying those interests, the authors (editors of NEJM) reiterate past policies and frame a new policy. They ended up, eventually, requiring disclosure of all conflicts of interest, but not in this article.

Drazen, J. M. and G. Koski (2000). "To Protect Those Who Serve." *N Engl J Med* 343(22): 1643-1645.

Patients submitting themselves to a clinical trial are inherently vulnerable; they understand the risk associated with their reward. When these clinical trials are industry-sponsored and may contain ambiguous COIs, they are in direct conflict with the patients' interests and therefore violate the physician-patient bond. This article calls for physicians to consider this when enrolling patients in clinical trials.

Duyk, G. (2003). "Attrition and Translation." *Science* 302(5645): 603-605.

The recently published NIH Roadmap proposes that public-sector science should place increased emphasis on the development of new therapeutics and diagnostics based on the fruits of fundamental research. Such "translational research" activities, traditionally the province of the private sector, have long been compromised by high rates of attrition (failure during the course of preclinical or clinical development of therapeutics). Attrition has led to growing financial costs, as well as opportunity costs. The new focus offers a way to reverse these trends, especially if the scientific community can improve on its ability to reconcile molecular genetic research with integrative organ- and organism-based research.

Eichenwald, K. and G. Kolata (1999). When physicians double as entrepreneurs. Hidden interests: a special report. *NY Times* (Print). New York City: A1, C16-17. November 30, 1999.

A very important report worth noting and reading. It chronicles not only COI's in medicine, but also the culture around them, questioning whether physician-inventors can ethically promote their products. Although there is much to be gained from new technology and increased competition, much is lost when physicians ignore patient interests and focus on profits.

<http://query.nytimes.com/gst/fullpage.html?sec=health&res=9D07E6D6103FF933A05752C1A96F958260>

Elliott, C. (2001). "Pharma Buys a Conscience. Bioethicists increasingly find their work underwritten by pharmaceutical companies. Who passes on the ethics of ethicists?" *The American Prospect* 12(17): 16-20.

Do as I say, not as I do. Does that apply to bioethicists? Unfortunately developing a center on bioethics requires lots of money and the usual deep pockets, drug and other companies seen to be the most willing sources of funding. This article bears some of the funding sources of prominent bioethics programs and questions bioethicists' behavior in the face of drug company dependence. He also indicates support of IRB members, of the FDA and of bioethics consultants tends to build favorable reviews.

Field, K. (2004). Medical School Reaches Agreement with Cancer Survivors in Suit over Canceled Study. *The Chronicle of Higher Education*.

If a study promises a therapeutic regimen and the company decides that the agent is not worth pursuing from the preliminary data, it can cancel the study. The participants argued that they were promised a full course of treatment by the university and sued.

Friedberg, M., B. Saffran, et al. (1999). "Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology." *JAMA* 282(15): 1453-1457.

Recent studies have found that when investigators have financial relationships with pharmaceutical or product manufacturers, they are less likely to criticize the safety or efficacy of these agents. In this study of a number of oncology drugs of different kinds, when comparing company vs non-profit supported studies, it was found that overstatement of positive results were less of a problem than a reduced likelihood of reporting unfavorable qualitative conclusions.

Friedman, P. J. (2002). "The Impact of Conflict of Interest on Trust in Science." *Sci Eng Ethics* 8(3): 413-420.

This paper is a deep analysis of the corrosive effects of conflicts of interest on trust in science, with the public and even among investigators. This lack of trust can have an adverse effect on the scientific record as well. Disclosure, our major method of dealing with COIs is really inadequate even if it were well- and completely carried out. We need new rules and new approaches and the author discusses some possibilities. He points out that managing COIs is not institutions of learning's best suite and that institutions can get into COI problems themselves.

Gelijns, A. C. and S. O. Thier (2002). "Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections." *JAMA* 287(1): 72-77.

The authors attempt to present a balanced account of the great benefits associated with Industry-Academic collaborations in research and development and the negative impacts of the relationships. This paper reviews institutional patterns of innovations and suggests organizational and public policy implications. This is important reading because many of the papers in this area deal with the negative aspects of university-industry relations and do not deal with the importance of these collaborations for advances.

Hahn, R. (2002). "Conflicts of Interest and the False Comfort of "Full Disclosure"." *Professional Ethics Report* 15(4).

The concept that revealing conflicts of interest in all presentations and publications eliminates their insidious effects on research. Not true, this article claims. The problem is that other mechanisms of control severely limit the incomes of successful scientists.

Hall, S. S. (2001). *Claritin and Schering-Plough: A Prescription for Profit*. The New York Times. New York. March 11, 2001.

This article purports to show that Schering used inadequate science to demonstrate that a mediocre antihistamine was less soporific than the older variety and therefore supplanted the older versions-at great cost to society. Ironically, branded claritin sells well as an over-the-counter antihistamine even though it is expensive.

Hart, D. (2002). "The "Corporatization" of Science." *Science* 295: 439.

This letter reviews the history of the support of basic research after WWII and reviews the changes in the scientific community that supported Bayh-Dole and indicated the importance of continuing attention to the new relationships developing as a result.

Horton, R. (2004). "The Dawn of McScience." *The New York Review*.

This review of Seldon Krimsky's book *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* The reviewer indicates that Krimsky produced a polemic indicating that declaring conflicts of interest will not solve the problems but that the separation of science from industry never truly existed and that, to some extent, the moral requirement to tell the truth in science was always blemished when it related to practical products. The Nancy Oliveri case, as well as the purchase of investigators and physicians by gift giving of pharmaceutical houses, are thoroughly discussed. I think that we are moving in the direction of balance by now, but my naivete may be showing.

Johns, M. M. E., M. Barnes, et al. (2003). "Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest: Promoting Research While Maintaining Trust." JAMA 289(6): 741-746.

This paper deals with University-Industry relationships from the point of view of the research managers and other leaders at academic institutions. The authors discuss divestiture, firewalls and other methods to ensure that industrial affiliations do not corrupt the activities of the university and adversely affect the public trust.

Johnston, J. (2004). "Outing the Conflicted: Et Tu, NIH?" Science 303(5664): 1610b-.

This report outlines the findings on NIH senior investigator and administrator conflicts of interest and their potentially serious consequences.

Kaiser, J. (2004). "BIOMEDICAL RESEARCH: Feeling the Heat, NIH Tightens Conflict-of-Interest Rules." Science 305(5680): 25-26.

This news article describes the first responses of NIH administration to revelations about intramural conflicts of interest.

Kaiser, J. (2004). "NATIONAL INSTITUTES OF HEALTH: Paid Consulting: Good for the Staff, Not for the Chiefs." Science 304(5673): 936a-937.

A news report on the extent of NIH staff involvement in conflicts of interest.

Kaiser, J. (2005). "CONFLICT OF INTEREST: NIH Chief Clamps Down on Consulting and Stock Ownership." Science 307(5711): 824-825.

A news report on the NIH ruling on conflicts of interest among its employees.

Kassirer, J. P. and M. Angell (1993). "Financial Conflicts of Interest in Biomedical Research." N Engl J Med 329(8): 570-571.

An early voice indicating the growing involvement of with industry and the conflicts of interest and of commitment they engender. Worthwhile reading.

Kassirer, J. P. and M. Angell (1997). "The High Price of Product Endorsement." N Engl J Med 337(10): 700-.

Product endorsement by a professional or scientific organization raises serious ethical problems. The endorsement is worth a lot to the product's company and it is willing to pay well for it. The question is whether the organization has done the comparative testing to determine whether this is a superior product worth endorsing. Organizations take risks to their credibility and financial risks when they endorse a product.

Kjaergard, L. L. and B. Als-Nielsen (2002). "Association between competing interests and authors' conclusions: epidemiological study of randomized clinical trials published in the BMJ." BMJ 325(7358): 249-.

To assess the association between competing interests and authors' conclusions in randomized clinical trials the authors conducted an epidemiological study of randomized clinical trials published in the BMJ from January 1997 to June 2001. Financial competing interests were defined as funding by for profit organizations and other competing interests as personal, academic, or political. They reviewed 159 trials from 12 medical specialties. Authors' conclusions were significantly more positive towards the experimental intervention in trials funded by for profit organizations alone compared with trials without competing interests, trials funded by both for profit and non-profit organizations, and trials with other competing interests. The authors' conclusions were that randomized clinical trials significantly favored

experimental interventions if financial competing interests were declared. Other competing interests were not significantly associated with authors' conclusions.

Krimsky, S. and L. Rothenberg (1998). "Financial interest and its disclosure in scientific publications." *JAMA* 280(3): 225-6.

Journal policies and requirements of funding agencies on financial disclosure of authors and grant applicants have divided editors and scientists who disagree on whether such policies can improve the integrity of science or manage conflicts of interest. Those opposed to such disclosure policies argue that financial interest is one of many interests held by scientists, is the least scientifically dangerous, and should not be singled out. Those who favor open reporting of financial interests argue that full disclosure removes the suspicion that something of relevance to objectivity is being hidden and allows readers to form their own opinions on whether a conflict of interest exists and what relevance that has to the study. The authors believe that the scientific community and the public will be best served by open publication of financial disclosures for readers and reviewers to evaluate.

Lawler, A. (2003). "UNIVERSITY-INDUSTRY COLLABORATION: Last of the Big-Time Spenders?" *Science* 299(5605): 330-333.

This review of the fate of large corporate gifts for research to universities suggests that the universities continued to do their thing but that the yield of marketable products to the dopanies was small. He concludes that on balance the agreements were win-win.

Levinsky, N. G. (2002). "Nonfinancial Conflicts of Interest in Research." *N Engl J Med* 347(10): 759-761.

The author considers his longstanding interest in his career and how that might have affected his objectivity in research. A worthwhile read.

Lo, B., L. Wolf, et al. (2000). "Conflict-of-interest policies for investigators in clinical trials." *N Engl J Med* 343(22): 1616-20.

There is substantial concern that financial conflicts of interest on the part of investigators conducting clinical trials may compromise the well being of research subjects. They analyzed policies governing conflicts of interest at the 10 medical schools in the United States that receive the largest amount of research funding from the National Institutes of Health. All 10 universities required that faculty members disclose financial interests to university officials. They conclude that policies governing conflicts of interest at leading medical schools in the United States vary widely. We suggest that university-based investigators and research staff be prohibited from holding stock, stock options, or decision-making positions in a company that may reasonably appear to be affected by the results of their clinical research. Of the 10 medical schools we studied, only 1 had a policy that was close to this standard.

Martin, J. B. and D. L. Kasper (2000). "In Whose Best Interest? Breaching the Academic-Industrial Wall." *N Engl J Med* 343(22): 1646-1649.

McCarthy, M. (2000). "Conflict of interest taints vaccine approval process, charges US report." *The Lancet* 356(9232): 838.

McCrary, S., C. Anderson, et al. (2000). "A national survey of policies on disclosure of conflicts of interest in biomedical research." *N Engl J Med* 343(22): 1621-6.

Conflicts of interest pose a threat to the integrity of scientific research. The current regulations of the U.S. Public Health Service and the National Science Foundation require that medical schools and other research institutions report the existence of conflicts of interest to the funding agency but allow the institutions to manage conflicts internally. They surveyed all medical schools (127) and other research institutions (170) that received more than \$5 million in total grants annually from the National Institutes of Health or the National Science Foundation; 48 journals in basic science and clinical medicine; and 17

federal agencies in order to analyze their policies on conflicts of interest. There was a very high response rate.. Fifteen of the 250 institutions (6 percent)--5 medical schools and 10 other research institutions--reported that they had no policy on conflicts of interest. Among the institutions that had policies, there was marked variation in the definition and management of conflicts. They concluded that there is substantial variation among policies on conflicts of interest at medical schools and other research institutions. This variation, combined with the fact that many scientific journals and funding agencies do not require disclosure of conflicts of interest, suggests that the current standards may not be adequate to maintain a high level of scientific integrity.

Moses, H., III, E. Braunwald, et al. (2002). "Collaborating with Industry -- Choices for the Academic Medical Center." *N Engl J Med* 347(17): 1371-1375.

This is a core paper that defines the issues in the various relationships between industry and academic medical centers. They take a drastic step in outlawing (at Harvard) most conflicts of interest with industry.

U. S. G AO (2003). University Research: Most Federal Agencies Need to Better Protect against Financial Conflicts of Interest. G. A. Office.

This extensive study of Federal agencies and universities indicated that at the time of the report protection against conflicts of interest was inadequate. Among Federal agencies only the NIH and NSF had policies requiring review and reporting of conflicts of interest related to research support.

Orlowski, J. and L. Wateska (1992). "The effects of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch." *Chest* 102(1): 270-3.

They examined the impact on physician prescribing patterns of pharmaceutical firms offering all-expenses-paid trips to popular sunbelt vacation sites to attend symposia sponsored by a pharmaceutical company. Drug usage patterns were tracked for 22 months preceding each symposium and for 17 months after each symposium. Ten physicians invited to each symposium were interviewed about the likelihood that such an enticement would affect their prescribing patterns. A significant increase in the prescribing pattern of both drugs occurred following the symposia. These changed prescribing patterns were also significantly different from the national usage patterns of the two drugs by hospitals with more than 500 beds and major medical centers over the same period of time. These alterations in prescribing patterns occurred even though the majority of physicians who attended the symposia believed that such enticements would not alter their prescribing patterns.

Patricia, B., D. Jocelyn, et al. (2002). "MEDICINE: Clinical Trials and Industry." *Science* 297(5590): 2211-.

Royal Australasian College of Physicians (2000). Ethical Guidelines in the Relationship Between Physicians and the Pharmaceutical Industry.

The Australians were able to agree on a set of ethical guidelines related to physicians and the pharmaceutical industry. They were opposed to most forms of gifts and proposed a skeptical position. It was not clear the extent to which these guidelines penetrated the profession..

Psaty, B. M., C. D. Furberg, et al. (2004). "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis." *JAMA* 292(21): 2622-2631.

In recent years, US patients have increasingly been the first to receive new medications, some of which are subsequently discovered to have suspected adverse drug reactions (SADRs). As a result, the challenge of early detection has largely shifted to the US postmarketing systems. They sought to review the association between the use of cerivastatin sodium and the risk of rhabdomyolysis in an effort to illustrate the operation and limitations of the current US postmarketing safety-surveillance system. In the published literature, cerivastatin was associated with much larger risks of rhabdomyolysis than other statins. Analyses suggested that compared with atorvastatin calcium, cerivastatin monotherapy substantially increased the risk of rhabdomyolysis. To our knowledge, these findings were not disseminated or published. The company continued to conduct safety studies, some of them inadequately designed to assess the risk of rhabdomyolysis, until cerivastatin was removed from the market in August 2001. They concluded that

despite limitations of the available data, the asymmetry between the information available to the company and the information available to patients and physicians seems striking. A subjective element is present in the effort to infer whether or not the occurrence of untoward outcomes in users of a particular drug was actually the consequence of the use of that drug, and, under the current system, a pharmaceutical company's appraisal of SADR's may be influenced by economic considerations. Such an appraisal would best be made by an independent group. They claim US Congress should mandate and provide adequate support for independent reviews and analysis of postmarketing data.

Psaty, B. M. and D. Rennie (2003). "Stopping Medical Research to Save Money: A Broken Pact With Researchers and Patients." JAMA 289(16): 2128-2131.

This report documents a case in which a drug company decided that its cancer drug was no longer worth developing and stopped a trial even though they had promised a longer trial in writing. Both the company and the institution were sued.

Ramsay, S. (2001). "Online database reveals researchers' industry ties." The Lancet 357(9269): 1977.

This neat idea reveals the great extent to which those conducting clinical research have industry income associated with that activity. The list proceeds apace.

Roberts, T. G., Jr. and B. A. Chabner (2004). "Beyond Fast Track for Drug Approvals." N Engl J Med 351(5): 501-505.

Clinical Trials. Deals with fast track mechanism and the importance of selecting probable responses to each new drug. Proposes "selective approval mechanism."

Scherer, F. M. (2004). "The Pharmaceutical Industry -- Prices and Progress." N Engl J Med 351(9): 927-932.

This report examines the cost and pricing structures of pharmaceutical companies and tries to deal constructively with the demands for lower prices while at the same time supporting costly research. It is a very worthwhile read.

Schulman, K. A., D. M. Seils, et al. (2002). "A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors." N Engl J Med 347(17): 1335-1341.

Concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) has issued revised guidelines for investigators' participation in the study design, access to data, and control over publication. It is unclear whether research conducted at academic institutions adheres to these new standards. From November 2001 through January 2002, they interviewed officials at U.S. medical schools about provisions in their institutions' agreements with industry sponsors of multicenter clinical trials. The results demonstrated limited adherence to the standards embodied in the new ICMJE guidelines. Scores for coordinating-center agreements were somewhat higher for most survey items. They suggest that a reevaluation of the process of contracting for clinical research is urgently needed.

Univ. of California_Senate. (2004). Report of the University Committee on Research Policy: Problematic Restrictive Clauses in Contracts, Grants and Gifts for Research, University Committee on Research Policy.

Steinbrook, R. (2004). "Conflicts of Interest at the NIH -- Resolving the Problem." N Engl J Med 351(10): 955-957.

This intermediate report discusses the various ideas that were considered at the NIH in an attempt to silence criticism while maintaining leeway for extra income for investigators.

The, Editor. (2004). "Publishing Commentary by Authors with Potential Conflicts of Interest: When, Why, and How." Ann Intern Med 141(1): 73-74.

This describes their policies at the time.

Weiss, R. (2004). NIH Bans Collaboration With Outside Companies. Washington Post. September 24, 2004.

This was the first response to the revelations of the extent of conflicts of interest at the NIH.

Williams, S. (2002). "Handle With Care: Avoiding Financial Conflict of Interest in Clinical Research." *Academic Physician and Scientist* January/February: 1, 10-12.

This paper begins by discussing the plight of the Fred Hutchinson Cancer Research Center when sued by research subjects' families. The issue of the Center or its physicians deriving financial benefit from the research put the organization in a weak position. This has led to the two AAMC reports on individual and institutional conflicts of interest that are referred to elsewhere in this bibliography.

Willman, D. (2001). Risk Was Known as FDA OKed Fatal Drug. *Los Angeles Times*. Los Angeles, CA. March 11, 2001.

The article chronicles Warner-Lambert's push and subsequent approval of the kidney drug Rezulin. Although liver damage was apparent in the clinical trial, Warner-Lambert's "partnership" with the FDA allowed for swift authorization. This should be a warning to all regulatory bodies about attaching themselves too closely to studies.

Willman, D. (2003). Stealth Merger: Drug Companies and Government Medical Research. *Los Angeles Times*. Los Angeles: A1, A32. December 7, 2003.

Some of the National Institutes of Health's top scientists are also collecting paychecks and stock options from biomedical firms. Increasingly, such deals are kept secret.

Willman, D. (2004). The National Institutes of Health: Public Servant or Private Marketer? *Los Angeles Times*. Los Angeles, CA: A29. December 22, 2004.

Another in a series of Willman's articles that deals with conflicts of interest. This one points out key scientists in the NIH with blatant COIs and the effect this has on research.

Willman, D. (2005). NIH to Ban Deals With Drug Firms. *Los Angeles Times*. LA, CA: A1, A17. February 1, 2005.

After initially breaking the COIs at the NIH, Willman announced the ban placed on industry-physician consulting relationships as well as other financial interests. These two Willman pieces on the NIH were monumentally influential in bringing to light gross inconsistencies in policy and their negative effects on the public.

Ziegler, M., P. Lew, et al. (1995). "The accuracy of drug information from pharmaceutical sales representatives." *JAMA* 273(16): 1296-8.

To provide quantitative data about the accuracy of the information about drugs presented to physicians by pharmaceutical sales representatives the authors investigated one hundred six statements about drugs made during 13 presentations by pharmaceutical representatives. Statements were rated inaccurate if they contradicted the 1993 Physicians' Desk Reference or material quoted or handed out by the sales representative. They found that twelve (11%) of 106 statements about drugs were inaccurate. All 12 inaccurate statements were favorable toward the promoted drug, whereas 39 (49%) of 79 accurate statements were favorable. None of 15 statements about competitors' drugs were favorable, but all were accurate, significantly differing from statements about promoted drugs. In a survey of 27 physicians who attended these presentations, seven recalled a false statement made by a pharmaceutical representative, and 10 said information from the representatives influenced the way they prescribed drugs. They claim that eleven percent of the statements made by pharmaceutical representatives about drugs contradicted information readily available to them. Physicians generally failed to recognize the inaccurate statements.

Brennan, T. A., D. J. Rothman, et al. (2006). "Health Industry Practices That Create the physician's roles Conflicts of Interest: A Policy Proposal for Academic Medical Centers." *JAMA* 295(4): 429-433.

Conflicts of interest between physicians' commitment to patient care and the blandishments that pharmaceutical companies and their representatives lavish on them impair professionalism in medicine. Although the involved groups, including the Federal government have instituted self-regulation of marketing, research into gift receipt and giving indicates that current controls will not satisfactorily protect the interests of patients. More stringent regulation is necessary, including the elimination or modification of

common practices. They propose a policy for academic medical centers to take the lead in eliminating these conflicts of interest that impair patient care.

Stossel, T. (2005). Mere Magazines. *The Wall Street Journal*. Washington, DC: A16. December 30, 2005.

In this brief article Dr. Stossel raises important questions about the arrogance of major medical journals and their persistent negative attitude towards the companies that are responsible for all the advances in medicine that we have seen over the past half-century. Whether or not you end up agreeing with the arguments, this is a refreshing contrast with the uniformity of the beating big Pharma has been taking in the medical literature and the media.

(2004). Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. DHHS. Services, Federal Register. 69 (92): 26393-7.

This federal guideline asks IRBs and institutions to consider a variety of means to eliminate, document, disclose, and manage conflicts of interest. It is not overly prescriptive but it expects institutions to actively and effectively deal with conflicts of interest both of individual investigators and of IRB members. Conflict of interest committees distinct from IRBs are expected to be developed. Required reading for research administrators.

Brody, B., C. Anderson, et al. (2003). "Expanding Disclosure of Conflicts of Interest: Views of Stakeholders." *IRB Ethics and Human Research* 25(1): 1-8.

Kim, S. Y. H., R. W. Millard, et al. (2004). "Potential research participants' views regarding researcher and institutional financial conflicts of interest." *J Med Ethics* 30(1): 73-79.

This empirical study of the attitudes of potential research subjects towards the revelation of financial conflicts of interest and their existence gave strong evidence that subjects wanted to know. Some would be less inclined to participate in the proposed study knowing of the conflicts of interest. A very nice study.

<http://jme.bmjournals.com/cgi/content/full/30/1/73>

Taylor, R. and J. Giles (2005). "Cash interests taint drug advice." *Nature* 437(7062): 1070.

This paper and the accompanying editorial deal with groups empanelled by professional societies primarily to write "evidence based" clinical practice guidelines. A study by Maternal found that substantial number of the panel members receive income or own stock in companies whose products are under consideration. The influence of these companies may be indirect in promoting drug use in the field or to encourage use of a specific product. Better methods of developing guidelines are suggested.

<http://www.nature.com/nature/journal/v437/n7062/full/4371070a.html>

Brody, H. and F. G. Miller (2003). "The clinician-investigator: unavoidable but manageable tension." *Kennedy Institute of Ethics J* 13(4): 329-46.

This paper addresses the two roles of the Clinician-Investigator as scientist and caregiver. The authors indicate that research is very different from care and thus there is ethical tension in doing both (the difference position). Those that argue that the physician's role is similar in both circumstances (similarity position) are claimed to be in error because the position denies the ethical tension. A very worthwhile read.

Mello, M. M., B. R. Clarridge, et al. (2005). "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry." *N Engl J Med* 352(21): 2202-2210.

This critical paper delineates the weaknesses of academic institutions in writing contracts that protect data and investigators from bias. This is very important reading.

<http://content.nejm.org/cgi/content/abstract/352/21/2202>

(2003). "American Society of Clinical Oncology: Background for Update of Conflict of Interest Policy." *J Clin Oncol* 21(12): 2387-2393.

The new version of their conflict of interest policy that is based on complete disclosure and a number of prohibitions. A good set of rules that others could emulate.

<http://www.jco.org/cgi/content/full/21/12/2387>

Bentley, J. P. and P. G. Thacker (2004). "The influence of risk and monetary payment on the research participation decision making process." *J Med Ethics* 30(3): 293-298.

This questionnaire study attempted to determine the impact of various levels of payment on willingness to participate in a trial. Knowledge of the characteristics of a trial and whether it would lead to behavior damaging the quality of the study. Money was an incentive. The other effects did not seem to be present.

<http://jme.bmjournals.com/cgi/content/full/30/3/293>

Miller, F. G. and A. F. Shorr (2002). "Ethical Assessment of Industry-Sponsored Clinical Trials*: A Case Analysis." *Chest* 121(4): 1337-1342.

These authors review a single randomized control trial of asthma therapy in children for its ethical characteristics and find it faulty. This is worthwhile reading.

<http://www.chestjournal.org/cgi/content/abstract/121/4/1337>

Schroter, S., J. Morris, et al. (2004). "Does the type of competing interest statement affect readers' perceptions of the credibility of research? Randomised trial." *BMJ* 328(7442): 742-743.

<http://bmj.bmjournals.com/cgi/content/full/328/7442/742>

An empirical study noting a competing financial interest on receiving research support on various aspects of a study. Believability and relevance were both significantly reduced in the presence of a financial conflict. All in all, a weak paper, but provocative.

Resnik, D. (2004). "Disclosing conflicts of interest to research subjects: an ethical and legal analysis." *Accountability in Research* 11(2): 141-59.

The author makes the case that investigators have an ethical and now a legal obligation to disclose their conflicts of interest in a manner such that the study participants will have enough information to sign an informed consent. He argues that disclosure of conflicts of interest should be required in informed consent documents.

Campbell, E., B. Moy, et al. (2004). "Institutional academic industry relationships: results of interviews with university leaders." *Accountability in Research* 11(2): 103-18.

The investigators conducted interviews of university leaders to get their viewpoints on academic-industry relationships. Generally, there were many such relationships and these were generally thought to be constructive. There was understanding that conflicts of interest were pervasive and sometimes risky.

Holmes, D. R., B. G. Firth, et al. (2004). "Conflict of interest." *American Heart Journal* 147(2): 228.

This report of an expert meeting reviews conflict of interest issues from the level of the investigator on to the FDA. It has become somewhat dated because of the recent NIH revelations and rule development and progress in registering clinical trials.

Bernstein, M. (2003). "Conflict of interest: It is ethical for an investigator to also be the primary care-giver in a clinical trial." *Journal of Neuro-Oncology* 63(2): 107.

The author addresses one of the issues of the day. He comes down in opposition to the AAME report on individual conflicts of interest in clinical research, as supporting such research in many instances.

<http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/A:1023959021758>

Komesaroff, P. (2005). "Ethical issues in the relationships with industry: an ongoing challenge. New Guidelines open for public comment." *J Paediatr Child Health* 41(11): 558-60.

In this paper the author explains the extent to which medical decision-making in Australia is influenced by industry. He provides guidelines to Australian physicians as to their behaviors, including the rejection of gifts, subsidized attendance at meeting, and samples. They should not endorse specific products. Clinicians should also avoid recruiting their patients into studies in which they are investigators, as well as only doing studies in which there is a commitment to make the results public. This should be followed by an empirical study on compliance.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1754.2005.00719.x>

Topol, E. J. and D. Blumenthal (2005). "Physicians and the Investment Industry." JAMA **293**(21): 2654-2657.

<http://jama.ama-assn.org/cgi/content/full/293/21/2654>

In this excellent paper the authors identify and discuss the new practice of clinical researchers providing information to investment groups as consultants. In a number of instances it appears that confidential information was leaked that gave investors significant advantages. The questions as to the ethical standing of this activity versus the right of professors to communicate about what they know was introduced. How can we be sure that the information is in the public domain before discussing it?

Weiss, R. (2004). NIH to Set Stiff Restrictions on Outside Consulting. Washington Post. Washington, D.C.: A01. August 4, 2004.

After a scandal revealed by the LA Times in which many NIH personnel including investigators and those with responsibilities for dispensing grants and contracts received substantial sums from drug and biotech companies the NIH took. Head of investigations by congress, internal reviews, and the report of an independent expert committee developed rules for NIH personnel. Familiar rules once being adopted by most major research institutions.

Chapter 5: Monitoring Research

Research by its very nature is a trip into the unknown for the subjects as well as for the entire investigator team. While the IRB has some monitoring responsibilities, it is not constituted so as to visit sites, examine data, interact with subjects, or make decisions as to the nature of an adverse event. In fact, IRBs function largely on trust; trust that the investigators will carry out the study according to protocol, trust that the data will be collected carefully, trust that the interests of the subjects will be primary and supercede those of the research, and trust that the investigators' conflicts of interest will not interfere with or bias the study. Research catastrophes have led to the conclusion that trust is not enough. Several kinds of research monitoring have evolved to deal with these issues.

1. Clinical Trial Monitors:

Sponsored clinical trials have monitors who make sure that the primary data are collected and recorded properly. They meet periodically with research coordinators and review their study records. They ensure that the reporting of adverse events is complete. This very useful auditing function serves to promote Good Clinical Practices and to enhance the compulsive collection of data. It is required by the FDA, which does not like to review incomplete studies. These monitors do not relate to the subjects.

2. Data and Safety Monitoring Boards (DSMBs):

In 1998 the NIH wrote policies for Data and Safety Monitoring Boards for studies supported by its Institutes and Centers. The report can be found at:

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

Key elements are replicated here but the entire policy is brief.

It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Although there are potential benefits to be derived from participation in clinical research, the IRBs and the NIH must ensure, to the extent possible, the safety of study participants and that they do

not incur undue risk and that the risks versus benefits are continually reassessed throughout the study period.

All clinical trials require monitoring -- Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III); etc.

Monitoring should be commensurate with risks -- The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.

Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

Double blinded randomized trials need intermediate assessment of both efficacy and safety as they progress. DSMBs are now constituted to carry out that function for both commercially sponsored and Federally sponsored clinical research. They are required for therapeutic studies. We expect that DSMB members be expert in the various aspects of a trial and include the capacity for sophisticated statistical analysis. DSMB members should be independent of the research and have no conflicts of interest in relation to the research. DSMB deliberations contain open and closed portions. In the closed portions, the blinding is removed to determine whether one experimental group is experiencing significantly greater efficacy or adverse events than others. DSMB members sign non-disclosure agreements and must maintain the highest degree of confidentiality in regard to their deliberations.

DSMBs have been known to stop trials early either because of established efficacy to the tested agent or increased risks associated with one arm of the trial. Such actions must be taken cautiously and with great care, considering the huge investment made by participants, investigators and sponsors alike. However, the DSMB is hopefully expert and objective in its deliberations. DSMBs have stopped the Women's Health Initiative, the NIDDM diabetes study, and the study of XXXX for breast cancer among others. They constitute a strong force for maintaining the ethical conduct of clinical research and are increasingly utilized. However, DSMBs have no direct contact with research subjects.

3. Research Subject Advocacy:

In 2001 the National Center for Research Resources established research subject advocates (RSAs) in all General Clinical Research Centers (GCRCs) funded by the NIH. These individuals were charged to develop a program of monitoring research carried out on the GCRCs, advocating for the subjects, and educating the research team as to their performance and ethical responsibilities. The RSA has access to the research participants, the protocols, DSM reports and the research team. The RSA ensures proper reporting and documentation of adverse events and protocol violations. Considerable information has been generated indicating that research errors are common and that the basis is often ignorance of standards, definitions and rules. The other main source of nonadherence is logistical problems in actually carrying out the research. These unanticipated problems can lead to protocol violations in order to get the research done.

4. Cancer center review:

Cancer Centers are provided funds for staff to monitor all the research that is under their auspices. They provided auditing functions as well as scientific and data and safety monitoring review.

5. Gene Therapy:

Gene therapy protocols undergo periodic audits and must be approved by the RAC in addition to all standard reviews.

6. Stem cell research:

Stem cell research is being monitored both by IRBs and by specially constituted ESCRO (embryonic stem cell research oversight) committees. The research will be carefully monitored and the use of the stem cells audited in detail, to some extent due to societal sensitivity to the abuse of the research material.

Cases Chapter 5

Case: Regulatory Controls and Career Success

Dr. Atkins is finally beginning to enjoy the success of her hard work on angiogenesis factors in cancer biology. Her work on HTGF (hypoxic tumor growth factor) led directly to her discovery of the HTGF receptor for which the active site was easily identified.

She had gone early to the Office of Intellectual property, which got patent protection for HTGF and its receptor as well as the use of its active site. It was suggested that Dr Atkins form a company and license back the rights to develop her discoveries but she decided that she was enjoying her life, did not want further complications and could help a commercial firm develop the therapeutic agent.

A major cancer-oriented biotechnology company Betagen, licensed Dr. Atkins' technology for a considerable sum. Although the company preferred to pay in cash, both the university and Dr. Atkins wanted and received a significant amount of equity, predicting that development of HTGF antagonists will be very profitable.

Betagen then asked Dr. Atkins to be a major consultant to them. Her knowledge was worth \$50,000 a year for monthly one day visits. They could pay her in cash or stock. It was up to her.

After two years of hard work, with Atkins' insights, the appropriate antagonist was synthesized and tested extensively in animals. Phase 1 and 2 trials in HTGF-over expressing lung carcinoma, one of the leading target cancers were completed.

Dr. Atkins is an oncologist specializing in lung cancer. She belongs to the departmental practice plan. She was approached by the contract clinical trials organization handling the HTGF antagonist to be the local PI for the definitive Phase 3 trial. She agreed to participate because she really wanted her patients to experience the benefits of her basic research. She wanted to be a truly translational investigator, so it was arranged.

She presented the research protocol to the IRB and Conflict of Interest Review Committee (CIRC) for approval.

The CIRC is concerned about her multiple roles – inventor, consultant, and PI and feels that there needs to be some accommodation made if the University is to accept the contract. She seeks a solution that will give her patients access to the trial.

The Contract and Grant Officer signs the contract for the University. Dr. Atkins and all her co-investigators also sign the contract indicating that they have read the agreement and will adhere to the terms including the confidentiality statement.

After the appropriate accommodation was made and the conflicts of interest noted in the informed consent document, the study was approved and began.

About 3 months into the 2 year accrual period, Dr Atkins saw a journal advertisement from Betagen offering basic research support for investigators studying cancer growth inhibition. She applied and was awarded \$100,000 annually for 3 years. Again, because of University rules Dr. Atkins had to provide the CIRC with information about her relationship to Betagen. She didn't understand why, since this basic science grant had nothing to do with the clinical trial and so she told her grant administrator to complete a negative disclosure form that she signed and submitted to the Contract and Grant Office with other grant paperwork.

Dr. Atkins was pleased to be called by a large investment group about a year into the study to consult with them about newer treatments for cancer. They would pay

\$2500 per hour for her time on conference calls. She considered this a perquisite of her success and participates about every 3 months.

Meanwhile, Betagen, anticipating the impending success of the trial, asks Dr. Atkins to join their Speakers Bureau to give oncologists a chance to hear her views on cancer therapy. She thought that this would give her greater exposure and prestige so she went to the speakers indoctrination meeting and was put on their list. She received numerous requests to give talks.

She has begun to realize that all these activities are beginning to cut into her family life and her basic research but she loves the recognition and respect.

Questions:

- 1. Dr. Atkins has entered the golden period of her career. Has her success created issues in relation to University rules and regulations?**
- 2. What issues have arisen in terms of her core career as a result of her success?**
- 3. What are her reporting responsibilities to the CIRC?**
- 4. What are her reporting requirements to her department?**
- 5. Do any of her activities put her career at risk?**

Case: Relations to Industry

Super Pharmaceuticals has been conducting a randomized double-blinded study of a revolutionary new treatment for osteoporosis at a major teaching hospital for the past 3 years; Dr. Miller is a major stockholder in the company and has been PI of this project at the hospital. He has 200 women over the age of 65 enrolled and he is enthusiastic about the drug. At the annual stockholders meeting the company disclosed positive findings, making the stock soar.

In a meeting with his Clinical Trials Coordinator Dr. Miller learns that two women in the study have developed a dilational cardiomyopathy. Dr. Miller informs the Data and Safety Monitoring Board, Super Pharmaceuticals and his institution's IRB of the SAE (serious adverse event).

The Data and Safety Monitoring Board reviews the data and reports simply that the study should continue because they believe the cardiomyopathy could not be clearly related to the drug. They send that report to the IRB and FDA. They do not require informing current and future study patients, or amending the protocol or Consent document.

Questions:

1. What are the issues in this case?
2. Is the institution at any risk here?
3. What do you believe the response should be to the serious adverse events?
4. How would you feel if Dr. Miller were studying mostly his own patients?
5. Were there any explicit or potential issues that might have affected initial approval of the study?

Case: Translational Research

Jones, a translational researcher in metabolism in a major academic department of medicine developed a small molecule PYY derivative that traverses the blood-brain-barrier and activates the satiety center. This anorexigenic agent has safely reduced appetite and weight in genetically obese mice and rats as well as normal animals, which became emaciated. Jones calls the product “Sleek.” Studies in other species demonstrated the unique effectiveness of Sleek.

Jones got Sleek patented by the university and founded a biotech company “ANOREX” to complete the clinical trials and market the product as well as to develop even better agents. Jones became CEO of the company and took an allocation of 25% of the stock. Obtaining venture capital funding was a snap.

Phase 1 and 2 clinical trials on obese patients in Jones’ metabolism clinic did not demonstrate any adverse effects and allowed the establishment of a dosage schedule adequate for a large Phase 3 clinical trial.

ANOREX engaged a clinical trials company to conduct the trial on Jones’ design in consultation with the FDA. Sleek would be given at two doses versus control to 500 individuals at greater than 100% above ideal body weight for 12 weeks in a double-blinded randomized manner. DEXA scans, weights, BP, and many chemistries would be done before beginning and at 1,3,6,9 and 12 weeks. Following completion of the initial trial, all participants would be placed on Sleek in an open label trial for six months. Jones would enroll 100 of the participants from his metabolic clinic to keep an eye on the study and the remainder will be enrolled in 20 cooperating sites.

Since Sleek is a new drug, Jones arranges a Data and Safety Monitoring Board consisting of the leadership of ANOREX and three of the other Principal Investigators, each of whom receives consulting fees from ANOREX.

All the participating IRBs approve the trial.

During the course of the 12-week trial, participants lose an average of two pounds weekly, are never hungry, and are delighted. A participant who works at a local newspaper asks Jones for an interview and he graciously gives an upbeat report in which the interviewer is cautioned that the trial remains in progress and is not conclusive.

During the open label portion of the trial two participants from Jones' metabolic clinic become ill. They develop congestive heart failure and, on hospitalization are found to have dilational cardiomyopathy. Sleek is stopped in both cases and the serious adverse event (SAE) is reported to the IRB and the FDA. However, the report claims that the drug was probably not the cause of the event since there were no reports of trouble at the other sites and idiopathic cardiomyopathy was not all that uncommon. One of the two patients improves rapidly and the other deteriorates to the point of requiring a heart transplant.

Questions:

- 1) Given the information provided, if you were an IRB member what questions would you have had for Jones prior to approval of the protocol?**
- 2) Would you have insisted on any changes to the trial?**
- 3) If you were the IRB chair, reading the SAE report, what further steps would you have insisted on?**
- 4) The Data and Safety Monitoring Board was scheduled to meet semi-annually. Should they have any further involvement in the process and if so what would you, as a member, insist on?**

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(2003). "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research." *Journal of Clinical Oncology* 21(12): 1-10.

Burman, W., R. Reves, et al. (2001). "Breaking the camel's back: multicenter clinical trials and local institutional review boards." *Ann Int Med* 134(2): 152-7.

This article, which has become historical by now described the lack of capacity of currently constituted IRBs to handle the increasing protocol load and also evaluate safety reports from large randomized clinical trials in a timely fashion. The rapidly rising number of multicenter clinical trials had put unprecedented stress on the institutions that was compounded by an increasing number of IRB investigations, often leading to publicly announced closures of major academic institutions' clinical research programs. They proposed a systematic investigation of the entire clinical research review process. This was carried out by the Institute of Medicine.

Cairns JA, Hallstrom A, et al. (2001). "Should all trials have a Data Safety and Monitoring Committee?" *Am Heart J* 141(1): 156-63.

This paper reviews development of DSM boards and explains the rationale for having their oversight. It reviews their functions and activities and ends by proposing a set of standards for appointment and charter of a DSMB.

Drazen, J. M. (2002). "Institutions, Contracts, and Academic Freedom." *N Engl J Med* 347(17): 1362-1363.

This editorial discusses contracting rules for clinical research carried out in academic institutions, focusing on insisting on the freedom to publish results no matter what they reveal.

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

Gamache, V. (2003). "Increasing Presence of Data Monitoring Committees." *Center Watch* 10(4): 1, 8-11.

This paper reports on the rise of Data and Safety Monitoring Boards as a further mechanism to oversee clinical research. Since then they have become almost ubiquitous.

Russo, E. (2000). "Monitoring Human Subjects and Clinical Trials." *The Scientist*: 6.

This news report indicates that IRBs are inadequate to monitor research even though they were given that mandate.

Slutsky, A. S. and J. V. Lavery (2004). "Data Safety and Monitoring Boards." *N Engl J Med* 350(11): 1143-1147.

(2003). "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research." *J Clin Oncol* 21(12): 2377-2386.

These are the 2003 American Society of Clinical Oncology rules and proposals for clinical research. These include centralized IRBs, standardized forms, and making informed consent documents more directed at informing about the study. They also promote more institutional support and education in ethical clinical research.

<http://www.jco.org/cgi/content/full/21/12/2377>

Andrews, J. (2006). "Research in the ranks: vulnerable subjects, coercible collaboration, and the hepatitis E vaccine trial in Nepal." *Perspect Biol Med* 49(1): 35-51.

The military are vulnerable subjects because requesting participation in research is, in itself, coercive. The example of the hepatitis E vaccine trial employing the Royal Nepal Army demonstrates the vulnerability of the soldiers.

http://muse.jhu.edu/journals/perspectives_in_biology_and_medicine/v049/49.1andrews.html

Hahn, S., P. R. Williamson, et al. (2002). "Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to a local research ethics committee." *Journal of Evaluation in Clinical Practice* 8(3): 353-359.

By comparing the initial protocol with the results and analysis of a small group of studies in Reading, U.K., the authors found that the primary objective was often not given and the analysis differed from that proposed. These results, if extrapolated, would indicate huge biases in clinical research.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2753.2002.00314.x>

Dominguez, R. A., D. J. Feaster, et al. (2005). "Searching for an efficient institutional review board review model: Interrelationship of trainee-investigators, funding, and initial approval." *Journal of Laboratory and Clinical Medicine* 145(2): 65.

These authors studied the IRB review process at their own institution to determine factors leading to delay in approval. They found that the presence of a trainee and the absence of external funding both were associated with delayed approval and suggested an educational intervention.

<http://www.journals.elsevierhealth.com/periodicals/ymlc/article/PIIS002221430400349X/abstract>

Judy Illes, et al. (2004). "Discovery and disclosure of incidental findings in neuroimaging research." *Journal of Magnetic Resonance Imaging* 20(5): 743-747.

This preliminary study identified the serious problem of incidental findings in brain imaging research. The findings may be quite important yet professional reading of the studies may be substantially delayed. Experimental designs should address the importance of a timely review of studies and reporting of coincidental findings.

Fisher, C. and S. Kornetsky (2005). "SACHRP recommendations for review of children's research requiring DHHS secretary's approval." *IRB* 27(3): 8-10.

These recommendations of SACHRAP, the Secretary's Advisory Committee on Human Research Protection, deal with the Federal 46.407 provisions to have control review of protocols that have more than minimal risk in pediatric research subjects.

Jones, A. M. and B. Bamford (2004). "The other face of research governance." *BMJ* 329(7460): 280-281. <http://bmj.bmjournals.com/cgi/content/full/329/7460/280>

Two descriptions of what happened when a protocol deviation was discovered and the research ethics office was notified. Was the response overkill or not?

Bhutta, Z. (2002). "Ethics in international health research: a perspective from the developing world." *Bulletin of the World Health Organization* 80(2): 114-20. [http://www.who.int/bulletin/archives/80\(2\)114.pdf](http://www.who.int/bulletin/archives/80(2)114.pdf)

This is an analysis of international research involving developing countries. He focuses on the elements that require discussion in the developing countries, including "standard of care" and prior agreements. The author also argues for more training in bioethics in developing countries and more focus on the public health measures that will do the most good for the population.

Korenman, S. and L. Shaker-Irwin (2003). Research Subject Advocacy--A New Way to Enhance Integrity in Clinical Research. *Endocrine Society News*. 1: 6-7.

The National Center for Research Resources provided General Clinical Research Centers funding to recruit and hire individuals to be Research Subject Advocates. The job description was somewhat vague. In this paper the authors describe their response to the charge to advocate for subjects and to oversee their research activities in a constructive manner. This describes how UCLA did it up to the date of the paper. This role has continued to evolve to include much more education, protocol monitoring, and face to face relationships with subjects and the research team.

Neill, K. (2003). "Research Subject Advocate: A New Protector of Research Participants." *Accountability in Research* 10(2): 159-74.

In October 2001 General Clinical Research Centers were funded to recruit Research Subject Advocates (RSAs). They rapidly developed their job descriptions in such a way as to help participants in clinical research throughout the experience. This paper describes the early days of the program.

Steinbrook, R. (2002). "Improving Protection for Research Subjects." *N Engl J Med* 346(18): 1425-1430.

A professional examination of the frailties of the clinical research process with attention to IRBs, DSMBs and other vehicles for accountability. This is one of a series of activities in various journals addressing the "crisis" in the process of clinical research identified by the serious failures occurring at Penn, John Hopkins, Rochester and other major research institutions.

Vincent, C. (2003). "Understanding and Responding to Adverse Events." *N Engl J Med* 348(11): 1051-1056.

In this essay the author focuses attention on the process of dealing with serious adverse events both as how to analyze them constructively to improve future performance and to support the participants, their families and the research team under these stressful conditions. He discusses system weaknesses as well as individual errors in the setting not of blame but of fostering improvement. Owning up to problem, truth-telling, and support are very important but prompt and thorough attention to harms done is essential to reestablishing confidence in the research team may also be seriously affected by a serious adverse event and should have an opportunity for expression and counseling if appropriate. This paper will really help the team to deal with a serious adverse event.

Marshall, E. (2000). "BIOMEDICAL ETHICS:Penn Report, Agency Heads Home In on Clinical Research." *Science* 288(5471): 1558-1559.

This report describes the response of Penn to the egregious problems in their clinical research activities revealed by the Jesse Gelsinger case. They are planning to use outside monitors for studies in which the institution has an interest. Furthermore their gene therapy institute would no longer do clinical trials. Both Penn and various Federal agencies indicated plans to more monitoring of clinical research.

Chapter 6: International Clinical Research

International clinical research is different from domestic research in developed countries because of the differing cultures of the researchers and the prospective subjects as well as because of their differing understandings of what will happen and why. It's easy to see why cultures with a daily fight for survival might find the issues of concern to the investigators quite foreign and puzzling. Yet, research must be done in low resource countries to deal with their medical problems, which differ from those of the developed world. Issues for the investigative team include:

A. Underlying conditions

- 1. Governments are less stable, insurgency may impair studies**
- 2. Protections for citizens are weak**
- 3. Disease portfolio, nutritional state, health care belief systems are different in developing countries and these differ from locale to locale**
- 4. Very rudimentary health care systems making it unlikely that study drugs will be affordable by the general population**
- 5. Serious logistical problems sometimes encountered in carrying out research, power, transportation, communication.**

B. Approval and Monitoring Issues

- 1. Requires an approved local IRB as well as an IRB from the sponsoring institution to approve the protocol and there are numerous misunderstandings and conflicts requiring a rational adjudication process. The IRBs and sponsors must agree on much more than in a developed country study.**
It is here that paternalism conflicts with national self-determination. There is conflict over whether controls should receive the developed nation standard of treatment rather than what would normally be available to them in their own country.
- 2. Studies require an effective Data and Safety Monitoring Board to adjudicate problems as well as to monitor the progress of the study but that might not be so easy to arrange.**
- 3. Adverse medical, social, and psychological events are not predictable but must be dealt with. Studies need a Standard Operating Procedure (SOP) for dealing with the unexpected.**

C. Study population issues

- 1. There are many vulnerable populations who might be study subjects especially with high illiteracy, limited exposure to the concepts of western medicine and to the idea of research.**

Major cultural differences must be understood sufficiently to avoid harm

- 2. There is often a requirement that the community or communities of the individual participants be involved in the research process during development as well as during execution.**
- 3. Investigators must avoid coercion through bribery, but food supplies, health care, etc. may be the equivalent of bribes in certain cultures.**
- 4. The consent process must be informational, understood, and voluntary and that's often difficult. Testing for comprehension is very helpful. Also the consent process must be repeatedly reiterated during the course of the study. It's worthwhile for the entire community to understand the research.**
- 5. There may be joint consent (with spouse) but the subject needs to receive health information privately and decide whether or how to present it to the other party.**
- 6. Development of health information about individuals must be dealt with exceedingly carefully as it can easily lead to stigmatization of individuals or of groups.**

D. Structural Issues

- 1. Obtaining and sustaining privacy and confidentiality may be a serious problem. Physical privacy for exams and questioning may be hard to find. Secure storage of data may be problematic. In certain cultures, the study personnel may be subject to intimidation to give up private information. Privacy extends to recruiting as well as to execution.**
- 2. Investigators must ensure that scarce health personnel and facilities are not usurped by a study to the detriment of local health care.**
- 3. Processing and transport of biological specimens may be problematic, especially if transported out of the country.**
- 4. It is highly desirable to utilize local personnel to help plan and manage the study and often this means a number of meetings and training sessions**
- 5. Often there is a requirement for a long-term continuation of care or technical support to the community but the degree and duration remain negotiable and if adverse events occur, the extent of required support might be extremely contentious. Community demands may not be affordable.**

E. Epidemiological and Social Science Research

- 1. These create new kinds of risks for social groups as well as individuals, including stigma, denial of access to health care, etc.**

2. In the epidemiological setting, ascertainment of the condition for the group may compete with privacy for the individual. The issue of societal need versus privacy commonly occurs with public health.
2. Clinical trials are more fraught with difficulty because of local issues. These include

- Ascertainment bias in design
- Bias in reporting
- Inappropriate access to data
- Adverse event reporting
- Appropriate monitoring
- Monitoring of Phase 1 and 2 trials

3. Protection of subjects. This includes:

- a) Assessing risks and benefits of treatments and of controls in the field
- b) Estimation of equipoise, individual and societal
- c) Data and safety monitoring in the field
- d) Social risks and psychological risks as they develop in the field. These may not be anticipated.
- e) Privacy and confidentiality in diverse communities with curious and meddling officials
- f) Therapeutic misconception of naïve subjects who don't understand the idea of research.

Cases: Chapter 6

Case: The Tawa

A previously unknown tribe in Papua-New Guinea, the Tawa was found to have an average adult height of 36 inches despite adequate nutrition. After the first report of discovery, the research community expressed an intense interest in studying the Tawa genetically, physiologically, sociologically, and psychologically as well as to determine whether they can be helped to attain greater height by medication.

Similarly, the media developed a most intense interest in televising the tribe to produce news stories and documentaries.

Access to these people was put under control of Papua-New Guinea Interior Minister who happened to be a physician educated in Australia. She wanted very much to do the right thing and was fearful that without careful control, chaos would ensue. An influx of Westerners however, would be a great shot in the arm to Papua New Guinea's weak economy.

She decides to hire you as the reigning expert to advise her and the tribe. You make a trip with your interpreter by jeep, donkey, and foot, mainly up hill and make acquaintance with the 80 members of the tribe.

You are sure that the tribe has a selective defect in the growth hormone-IGF₁ axis that will be very interesting, and that the tribe's isolation for many generations makes genomic study very interesting. It would also be valuable to use the opportunity of drawing blood to investigate their cardiovascular risk factors and susceptibility to infections.

In fact, the number of valuable studies immediately conceivable was enormous.

Questions:

- 1. Is it ethical to conduct research on the Tawa? Elaborate on the background issues that will help you to decide?**
- 2. The concepts of writing, blood drawing, research and questionnaires are unknown to the Tawa. Although they have language, it is limited to 500 words or so and does not include many specifics. How are you going to explain to them what research and genetic research are?**
- 3. The tribe is a vulnerable population. Is there a way of getting a surrogate to stand for them in understanding planned research?**
- 4. What will you write in your report to the Interior Minister?**

CASE: Research with Indigenous Tribe

Deep in the Brazilian jungle the Ogura tribe retains its ancient culture of nakedness, hunting, including the cannibalization of males from other villages and capturing females and children, as well as gathering edible vegetation and fishing in adjacent streams. The Ogura are big and strapping and seem to have a lot of children. However, very few Ogura can be found who appear older than around 50 years of age.

The Brazilian government has made extensive contact with indigenous cultures and has agents and translators who visit regularly and are accepted by the tribe. The government is concerned that tree poachers are destroying the jungle habitat for indigenous cultures. The Ogura, using lightning raids, have killed a number of poachers and, to date, have preserved their environment.

You, as a great public health and genetic researcher have been invited by the government to initiate genetic, anthropological and public health research into the tribe in hopes of helping them survive, either in their own environment or in the modern world.

You see this as a great but ethically challenging opportunity. You schedule a visit to the Ogura with the agent and translator.

Questions:

- 1. What issues would you like to cover in your visit?**
- 2. The desired information includes the blood of as many members of the tribe as possible to do genome analysis and determine whether there are clinical reasons for their apparent short life spans. What ethical issues arise as you consider how to do this?**
- 3. How will you go about conducting research on this population?**

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Bhardwaj, M. and D. Macer (2003). "Policy and ethical issues in applying medical biotechnology in developing countries." *Med Sci Monit* 9(2): RA49-54.

This is a discussion of the problems involved in developing medical technology, including drugs, in India. The authors consider issues with the research and adaptation of Western concepts of ethical clinical research. They also discuss political influences on research decisions including the battle between spending for prestige and spending to relieve the world problems.

Levine, R. (2000). "Some Recent Developments in the International Guidelines on the Ethics of Researching Involving Human Subjects." *Ann NY Acad Sci* November(918): 170-8.

The author carefully reviews the most controversial elements of the Declaration of Helsinki after strong wording had been inserted in relation to use of placebos. He argues both that the concepts of therapeutic vs. non-therapeutic studies and the prohibition of placebo use when effective agents exist are misleading and sometimes embarrassing in their implications.

Marshall, P. (2005). "Human Rights, Cultural Pluralism, and International Health Research." *Theoretical Medicine and Bioethics* 26(6): 529.

This thoughtful paper deals with the ethical obligations to consider human rights, socioeconomic, and political issues in conducting international health research, especially in resource-poor countries. Not only does there have to be a great deal of community input -- to the point of partnership, but physical resources and know-how have to be part of the package so that the community receives continued benefit from the research. One might consider some parts of the US as similarly deprived with similar needs. <http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11017-005-2199-5>

Cooley, D. R. (2001). "Distributive Justice and Clinical Trials in the Third World." *Theoretical Medicine and Bioethics* 22(3): 151.

This long philosophical paper addresses the claim that in international research in resource-poor countries, those who are non-participants are exploited. They, it is argued, are denied access to reasonable availability of the products of the research. This aspect of distributive justice is argued against in this paper. <http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/A:1011452716028>

Molyneux, C. S., D. R. Wassenaar, et al. (2005). "'Even if they ask you to stand by a tree all day, you will have to do it (laughter).'" Community voices on the notion and practice of informed consent for biomedical research in developing countries." *Social Science & Medicine* 61(2): 443.

This extremely interesting report was directed at the question of informed consent in a resource-poor area of Kenya where much research was done. They found, in asking who should be asked to give

consent that the answer was muddled by the persistent belief that the research was clinical care. This should be a lesson to those dwelling on the nuances of informed consent in such settings.

<http://www.sciencedirect.com/science/article/B6VBF-4FFN4N5-1/2/b7d785f694ea7703bdca485d4670769e>

Molyneux, C. S., N. Peshu, et al. (2004). "Understanding of informed consent in a low-income setting: three case studies from the Kenyan coast." *Social Science & Medicine* 59(12): 2547.

This really useful paper elaborates with specificity the issues surrounding acceptance of research activities in a very resource-poor environment in Kenya. The limited vocabulary to try to explain research leaves the participants trying to explain why it is that the researchers are doing what they do. There are exaggerated concepts of what such things as blood drawing can do to help individuals in studies designed to help populations. Very worthwhile.

<http://www.sciencedirect.com/science/article/B6VBF-4CKFGMR-3/2/c2f00be4516113128f7ec7f2c11f9a17>

Benatar, S. (2002). "Reflections and recommendations on research ethics in developing countries." *Soc Sci Med* 54(7): 1131-41.

Benatar, one of the grand elders of international ethics, discusses broad responsibilities for ethics review committees beyond informed consent and risk-benefit ratios. He believes that these committees should communicate at the community level, monitor research, and act to enhance the research capacity of each country by entering the political domain. These very perceptive remarks provoke considerable reflection.

Upvall, M. and S. Hashwani (2001). "Negotiating the informed-consent process in developing countries: a comparison of Swaziland and Pakistan." *Int Nurs Rev* 48(3): 188-92.

This study describes and analyzes the issues in protecting the rights of research participants in developing countries with emphasis on Pakistan and Swaziland. The main issues related to gatekeepers at all levels who were either eager to exercise control or to protect their positions. It emphasizes just how much prelim work had to be done before research could commence.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1466-7657.2001.00063.x>

Emanuel, E., W. D., et al. (2004). "What makes clinical research in developing countries ethical? The benchmarks of ethical research." *J Infect Dis* 189(5): 930-7.

The authors provide a comprehensive set of guidelines to investigators engaged in or considering research in developing countries. In these guidelines they elaborate in the communities (social) concerns in clinical research and the avoidance of exploitation using a 33 point table. This is a real contribution.

<http://www.journals.uchicago.edu/JID/journal/issues/v189n5/31380/31380.html>

Kirigia, J., C. Wambebe, et al. (2005). "Status of national research bioethics committees in the WHO African region." *BMC Medical Ethics* 6(1): 10.

This is a description of the research ethics committee status of the 46 countries in Sub-Saharan Africa that are related to WHO. IT indicates that only 2/3 have a research ethics committee (as of 2001) although 80% had some sort of review process. They propose that even the poorest country should set up a review system.

<http://www.biomedcentral.com/1472-6939/6/10>

Hyder, A. A., S. A. Wali, et al. (2004). "Ethical review of health research: a perspective from developing country researchers." *J Med Ethics* 30(1): 68-72.

This empirical study investigates the reality of clinical research carried out in developing countries sometimes in collaboration with US investigators. They found that many of the studies being carried out by over 600 investigators had no IRB approval and that many of the recommendations of the US National Bioethics Advisory Commission were not in effect for example, language-appropriate consent forms.

<http://jme.bmjournals.com/cgi/content/full/30/1/68>

Kottow, M. H. (2003). "The Vulnerable and the Susceptible." *Bioethics* 17(5-6): 460-471.

The author distinguishes the word vulnerable -- the underlying state of mankind requiring government to keep us from each other's throats; and susceptible -- a state of defective health that makes some of us ethically entitled to help others. Applied to research on humans, this applies to subjects from developing countries.

<http://www.blackwell-synergy.com/doi/abs/10.1111/1467-8519.00361>

Creed-Kanashiro, H., B. Ore, et al. (2005). "Conducting Research in Developing Countries: Experiences of the Informed Consent Process from Community Studies in Peru." *J. Nutr.* **135**(4): 925-928.

The authors present their experiences and raise questions about the meaning of informed consent and how the model of implementation could be changed.

<http://jn.nutrition.org/cgi/content/full/135/4/925>

Kass, N. E., L. Dawson, et al. (2003). "Ethical oversight of research in developing countries." *IRB: Ethics & Human Research* **25**(2): 1-10.

A unique survey conducted under the auspices of the NBAC studying researchers from developed countries perspectives on oversight of research in developing countries. They developed an instrument using focus groups. They identified appropriate researchers and got a 47% response rate. The results indicated beliefs of the investigators regarding the oversight of studies they were conducting in a number of domains. Well worth reading.

Dickens, B. M. and R. J. Cook (2003). "Challenges Of Ethical Research In Resource-Poor Settings." *International Journal of Gynecology & Obstetrics* **80**(1): 79.

This study focuses on reproductive studies of women from developing countries. It details barriers that are institutional, issues with informed consent, use of placebos, problems with ethics review committees, etc.

<http://www.sciencedirect.com/science/article/B6T7M-47MNYN7-G/2/8fb17bab203b70338b01aeb84eb01186>

Lie, R. K., E. Emanuel, et al. (2004). "The Standard Of Care Debate: The Declaration Of Helsinki Versus The International Consensus Opinion." *J Med Ethics* **30**(2): 190-193.

This brief paper reviews the controversy surrounding the limitations on clinical research resulting from the requirement of the Declaration of Helsinki year 2000 version's absolute requirement for the best standard therapy in controls of therapeutic trials. The authors point out that other groups give investigators more experimental design options. So, the debate over treatment options in studies in developing countries persists.

<http://jme.bmjournals.com/cgi/content/full/30/2/190>

7: Genetics and Stem Cell Research

A.Genetics

1. Introduction

The principal special feature of genetics research is that the result of the study applies not only to the proband but also influences her lineage both in the past and in the future. For example genetic studies demonstrated Thomas Jefferson's sexual relationship with his slave Sally Hemings and defined their descendants to this day. As we all know from television, genetic studies can be done from any tissue fragment that contains DNA so that studies of surgical specimens, biopsy materials, hair, epithelium and blood samples can all be utilized for extensive genetic studies.

2. Sampling

Some DNA is more medically valuable than other. Samples from isolated populations in which a particular disorder is prevalent have a much greater probability of yielding the causal gene(s) because they have fewer genome variations than in the general population. Once isolated, the genetic material associated with the disorder has a good chance of yielding novel diagnostic and/or therapeutic approaches for the disorder.

3. Property rights

A persistent question is whether the providers of the genetic material have any rights to the products created from their genetic material. These days, most consent forms are written explicitly to exclude intellectual property rights from the subjects. As might be imagined, this smacks of exploitation in the developing world. Negotiation of a monetary return to the community has sometimes been concluded. Important and lucrative products have been derived from individuals' genomes without their receiving royalties or other compensation. However, the knowledge, technical expertise, and capital needed to make a useful product from a blood or tissue sample come from the company not the donor.

4. Informed consent

Truly informed consent remains a problem with research subjects from both developed and developing countries. The sample providers may not understand the implications of genetic research for their families and their community. They surely don't understand the many uses to which their genetic material may be applied. They may not be aware that their genes may be used for pharmacogenetics. They are not likely to be fully cognizant of the forensic uses to which their genetic material might be put as our privacy rights continue to be eroded. They are putting their trust in the research establishment and the regulatory controls effected by the

IRB managing grant or contract. Contributors to repositories may not be fully aware of the fact that they are trusting scientifically-oriented review boards to determine how their genetic material will be used long into the future. While anonymization is of great help, in the future, the genome itself may serve to identify the person, especially if they are in more than one repository.

Informed consents for genetic studies using CLIA-approved tests are usually designed to give the subjects the option of finding out their susceptibilities or not. Subjects are told they will not get any feedback from tests that are in the developmental stages because the reliability of such tests is not known.

2. Insurance and stigmatization

In developed countries they might not perceive possible implications for stigmatization and for health and life insurability. Lack of health insurability affects Americans the most because every other developed country has a national health program. In those countries genetic information about disease risks motivates the system to preventive measures. In the U.S., revealing genetic information may exclude individuals from health insurance or make them join undesirable assigned risk pools. Thus knowing her susceptibilities may put a burden on the patient/subject to reveal what could be considered to be a preexisting condition. In fact, the rapidly increasing availability and declining costs of genetic information represent among the strongest arguments for a comprehensive health insurance program in the U.S.

3. Commoditization of genetic material

Patenting genetic material for development as medical tools raises the question of commoditization. Individuals from many countries but especially developing countries feel that their genome is an important component of their selves or souls. Just as some groups feel that they lose something if a photograph is taken of them, many feel that they may be compromised by genetic studies and the patenting of their individuality. In some environments, communities express the belief that there is no such thing as informed consent for genetic studies because the individual is speaking for his ancestors and descendants.

B. Human Embryonic Stem Cell Research

1. Introduction

Human embryonic stem cell (hESC) research is thought to have great potential in disorders in which cellular loss is known to occur. These include Type 1 diabetes mellitus, Parkinson's disease, and the post-myocardial infarction heart. Nevertheless, some believe that pre-implantation embryos are potential human beings with a soul making hESC research immoral. Human embryonic stem cell research raises other important ethical dilemmas as well. As a result of these ethical

and moral dilemmas the government has limited federally funding for hESC research to what has turned out to be 19 pre-existing “registered” cell lines (Sept. 2005). Private sources and states have been left to determine the extent to which they are prepared to support additional hESC research. A number of states, most prominently California, have decided to support research in this area.

2. What are embryonic stem cells and how do you make them?

The goal is to have stem cell lines derived from embryonic stem cells. Cells from these lines are “totipotent” because in theory, they can be transformed into any kind of tissue by the appropriate biological and chemical manipulations. Without going into detail and elaborating on all the limitations and caveats, embryonic stem cell lines can be created three ways.

a. Eggs and sperm can be obtained from donors, mixed in a Petri dish and the egg fertilized for the purpose of producing a stem cell line for research. The fertilized egg (zygote) divides into a multicellular embryo. With further incubation a blastocyst, a hollow ball of about 256 cells, is formed. The blastocyst has two kinds of cell groups, a group on the surface that is capable of initiating implantation into the uterus and becoming the placenta, and the inner cell mass with the capacity to become the fetus. The inner cell mass can be removed and encouraged to divide in culture medium. Under carefully defined conditions, these can be induced to become a cell line, dividing indefinitely. With proper chemical treatment the stem cells can, in theory develop into any tissue.

b. Annually, many thousands of infertile couples create embryos for in-vitro fertilization (IVF), by having their eggs and sperm mixed and fertilized in a petri dish. Usually the potential mother is stimulated with hormones and provides a number of eggs. Similarly, the potential father has millions of sperm in his ejaculated semen. Normally all the eggs are exposed to sperm and a number of become fertilized and become embryos. The best looking embryos are incubated long enough to become blastocysts. Usually three are implanted into the potential mother’s uterus. The remaining embryos are stored in liquid nitrogen in case of pregnancy failure or for later use if the family wants another child. These embryos are stored in cryobanks. Many of them eventually become available for research. With informed donor consent from both parents, these frozen embryos have the potential for providing most of the necessary raw material for stem cell research.

c. Somatic cell nuclear transfer (SCNT or just NT) was responsible for creating the sheep clone Dolly. In this process, young women donate ova by undergoing the “superovulation” process, as do infertile women. The egg has its nucleus containing the genetic material removed. The nucleus of an adult cell of research interest is

placed into the enucleated egg. By a remarkable process the adult nucleus dedifferentiates in the ovum from, say a skin cell, into a totipotent state and the ovum proceeds to divide and become a blastocyst. Its inner cell mass can be made into a stem cell line. This process has a theoretical advantage in that theoretically stem cells could be produced with any genetic condition of interest by introducing the nucleus from a person with the condition. The major disadvantage of NT is that a supply of human unfertilized eggs is required to do the research. Until a reliable source of human ova can be obtained without either a large payoff or by coercion, this process is unlikely to become the main source of embryonic stem cells. However, it is conceivable that mothers of individuals with a serious disorder such as Type 1 diabetes mellitus would be willing to donate eggs to further research progress.

A major ethical dilemma that has just grounded the highly successful Korean Stem Cell Institute was the provision of ova by laboratory workers who had a dependent relationship to the investigators and were therefore susceptible to coercion.

3. Ethical Issues

- a. The core issue related to hESC research is the status of the early embryo. Is it a human being with a soul that must be protected or is it a collection of cells that will not become part of humanity until a later time. This issue cannot be resolved on a scientific basis but rather plays a central role in religious and political differences within America.
- b. Unlike the use of zygotes containing the combined genetic material from a male and a female, as in IVF, NT results in a “clone” of the donor of the adult cell. Implanting such a blastocyst into a woman, termed “reproductive cloning,” would result in an individual with the exact genetic makeup of the donor of the nucleus. Agreement has been reached that reproductive cloning of humans is unethical and should not be permitted.
- c. NT, which to date is a very inefficient process, requires large numbers of donated ova from volunteers. In other research settings, volunteers may be paid for their trouble but must not be coerced into volunteering either by being dependent on the investigators or by enticing them with compensation. These same criteria are likely to hold for ovum donors although ovum donors for the treatment of infertility are being paid large amounts of money for their efforts.

- d. **Ovum donation is not a benign procedure. A sample consent form for ovum donation for hESC research purposes is given below.**

Bibliography

Genetics Research

Curzer, H. (2004). "The ethics of embryonic stem cell research." J Med Philos 29(5): 533-62.

This author analyzes the issues surrounding using human embryos to develop stem cell lines for research as a philosopher in a set of philosophical arguments that support the use of embryos and even the creation of embryos for research purposes.

Pennings, G. and A. Van Steirteghem (2004). "The subsidiarity principle in the context of embryonic stem cell research." Hum. Reprod. 19(5): 1060-1064.

<http://humrep.oxfordjournals.org/cgi/content/full/19/5/1060>

The authors deal with the "subsidiarity principal" that indicates human embryonic stem cell research should be a last resort to be utilized only if other research tools cannot do the job. After careful argument, they conclude that the burden should be on those who claim other research achieve the same scientific and humanitarian goals, considering the stakes for human life and well-being.

Scully, J. L. and C. Rehmann-Sutter (2001). "When Norms Normalize: The Case of Genetic "Enhancement"." Human Gene Therapy 12(1): 87-95.

<http://www.liebertonline.com/doi/abs/10.1089/104303401451004>

This philosophical paper addresses the question of treating to enhance versus treating to improve to normal. They claim that with the differences of opinion and difficulty characterizing normal, it would be better defining unethical enhancement by a better standard more related to the motivations for and consequences of the "enhancement."

Steinbrook, R. (2006). "Egg Donation and Human Embryonic Stem-Cell Research." N Engl J Med 354(4): 324-326.

<http://content.nejm.org/cgi/content/extract/354/4/324>

This paper describes the current status of egg donation for SCNT in stem cell research. The author focuses on the donor risks and the limited benefits that might accrue to the donor. The questions surrounding payment of donors are addressed in detail.

Snyder, E. Y. and J. F. Loring (2006). "Beyond Fraud -- Stem-Cell Research Continues." N Engl J Med 354(4): 321-324.

<http://content.nejm.org/cgi/content/extract/354/4/321>

This article published immediately after the Hwang debacle reiterates the self-corrupting characteristics of science and indicates that stem cell research has more challenges than it thought it had. The paper also attempted to assure the public that science and scientists were not all corrupt.

DeCamp, M. and J. Sugarman (2004). "Ethics in Behavioral Genetics Research." Accountability in Research 11(2): 27-47.

This excellent paper systematically reviews the special issues surrounding behavioral genetics research involving phenotypic designation, involvement of the community, and vulnerability. He also discusses the social obligations of the scientists to deal in advance with the potential of stigmatizing individuals and populations. He indicates some of the adverse consequences of poorly thought out earlier work.

Stem Cell research

Okie, S. (2005). "Stem-Cell Research -- Signposts and Roadblocks." N Engl J Med 353(1): 1-5.

(2000). Ethical Issues in Human Stem Cell Research. National Bioethics Advisory Commission. Volume III, Religious Perspectives.

This booklet contains ten brief thoughtful analyses of the stem cell issues from various religious perspectives. The articles contain in addition to the conclusions the religious rationale for them. This is an extremely worthwhile set of readings for those who, willingly or unwillingly, are entering the discussion of the research use of embryos.

(2000). "Statement on Gene Therapy, April 2000." *Am J Hum Genet.* 67(2): 272-3.

Abbott, A. (1999). "Sweden sets ethical standards for use of genetic 'biobanks'." *Nature* 400(6739): 3.

This report details Sweden's laws dealing with gene banks. There are rules for consent, reconsenting, privacy, ethical review of use of materials, and rules for non-exclusivity of materials.

Annas, G. J. (2001). "The limits of state laws to protect genetic information." *N Engl J Med* 345(5): 385-8.

In this report, the newly passed Massachusetts statute regulating the use of genetic information is discussed as an example of what states were doing. It covered consent, discrimination, privacy, etc. It revolved to a degree on the definition of genetic information and that's what makes it a very interesting paper.

Begley, S. (2004). Is Alzheimer's Field Blocking Research Into Other Causes? *Wall Street Journal*. April 9, 2004.

She discusses the role of favored theories in getting the bulk of research funding.

Streiffer, R. (2005). "At the edge of humanity: Human stem cells, chimera, and moral status." *Kennedy Inst Ethics J* 15(4): 347-70.

The author addresses in great detail the ethical issues that arise when considering the production of chimeras by introducing human pluripotent stem cells into other species. The core question is whether the moral standing of the recipient animal is enhanced and, if so, how to handle that. The world of entertainment is rife with creatures exhibiting human characteristics to whom we have assigned moral standing so this is not a trivial question in our society. Purely technical proposals might generate considerate concern.

Aguilar, L. K. and E. Aguilar-Cordova (2003). "Evolution of a Gene Therapy Clinical Trial." *Journal of Neuro-Oncology* 65(3): 307.

This is an excellent review of the promise and pitfalls of gene therapy trials. Specific examples are given to illuminate the issues. A very worthwhile paper.

<http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/B:NEON.0000003659.04633.6e>

Baylis, F. (2002). "Human embryonic stem cell lines: the ethics of derivation." *J Obstet Gynaecol Can* 24(2): 159-63.

The author points out that unusable embryos are relatively rare in Canada and should be utilized for important research. This lack could either impede research or create a demand for the purposeful creation of embryos for research. Interesting.

Christiani, D., R. Sharp, et al. (2001). "Applying genomic technologies in environmental health research: challenges and opportunities." *J Occup Environ Med* 43(5): 526-33.

This article describes the promise of molecular genetics in identifying environmental hazards and developing methods for analyzing, preventing, and treating exposures. They describe the ethical, legal, and social challenges in carrying out such studies.

Cohen, C. (2005). "Promises and perils of public deliberation: contrasting two national bioethics commissions on embryonic stem cell research." *Kennedy Inst Ethics J* 15(3): 269-88.

The author analyzes philosophically the ethical approaches of the two national bioethics commissions and finds suggestions as to how such commissions may have to operate in considering issues under public debate.

Beskow, L. M., W. Burke, et al. (2001). "Informed Consent for Population-Based Research Involving Genetics." *JAMA* 286(18): 2315-2321.

What follows is the abstract of a report by a group formed by the CDC to determine some rules for approaching population-based genetic research. Bridging the gap between gene discovery and our ability to use genetic information to benefit health requires population-based knowledge about the contribution of common gene variants and gene-environment interactions to the risk of disease. The risks and benefits associated with population-based research involving genetics, especially lower-penetrance gene variants, can differ in nature from those associated with family-based research. In response to the urgent need for appropriate guidelines, the Centers for Disease Control and Prevention formed a multidisciplinary group to develop an informed consent approach for integrating genetic variation into population-based research. The group used expert opinion and federal regulations, the National Bioethics Advisory Commission's report on research involving human biological materials, existing consent forms, and literature on informed consent to create suggested language for informed consent documents and a supplemental brochure. This language reflects the premise that the probability and magnitude of harm, as well as possible personal benefits, are directly related to the meaning of the results for the health of the participant and that appropriate disclosures and processes for obtaining consent should be based on an assessment at the outset of the likelihood that the results will generate information that could lead directly to an evidence-based intervention. This informed consent approach is proposed to promote discussion about how best to enable potential participants to make informed decisions about population-based research involving genetics and to suggest issues for consideration by research sponsors, institutional review boards, and investigators.

Clayton, E. W. (2003). "Ethical, Legal, and Social Implications of Genomic Medicine." *N Engl J Med* 349(6): 562-569.

This excellent article describes a number of cases in which genetic information formed the basis of legal action. She described the public's worries about the availability of their genetic information to insurance companies and government agencies, its use in forensic investigations, and its use for discrimination in employment, even for medically sound reasons. She describes state regulations. She presents the dilemmas in the physician-patient relationship. Very worthwhile reading.

Clayton, E. W., K. K. Steinberg, et al. (1995). "Informed consent for genetic research on stored tissue samples." *JAMA* 274(22): 1786-1792.

This somewhat dated report describes the results of a consensus development process arranged by the CDC. The diverse group involved concluded that consent was important unless samples were anonymized, that IRBs could usefully review proposals to use tissues, and that the matter was not settled.

Dickenson, D. (2004). "CONSENT, COMMODIFICATION AND BENEFIT-SHARING IN GENETIC RESEARCH." *Developing World Bioethics* 4(2): 109-124.

This is a very thoughtful and interesting paper. It deals with the issues surrounding getting blood or tissue samples for genetic diagnostics and for the development of treatments for diseases. These include the lack of informedness in the consent, especially about the potential economic benefits, the commodification of our bodies, which is somewhat distasteful and the nations of exploitation and bribery in getting samples from developing countries. There is also the question of the meaning of access to the results of the intervention.

Evers, K. (2002). "European perspectives on therapeutic cloning." *N Engl J Med* 346(20): 1579-82.

The author, an ethicist, proposes extensive international regulations to protect individuals from potential abuse as a consequence of experiments in therapeutic cloning. Therapeutic cloning most likely will involve somatic cell nuclear transfer and thus lots of donated ova. She worries about the commodification of human reproductive tissues, but does not come down for or against their use.

Fischbach, G. D. and R. L. Fischbach (2004). "Stem cells: science, policy, and ethics." *J. Clin. Invest.* 114(10): 1364-1370.

Human embryonic stem cells offer the promise of a new regenerative medicine in which damaged adult cells can be replaced with new cells. Research is needed to determine the most viable stem cell lines and reliable ways to promote the differentiation of pluripotent stem cells into specific cell types (neurons,

muscle cells, etc.). To create new cell lines, it is necessary to destroy preimplantation blastocysts. This has led to an intense debate that threatens to limit embryonic stem cell research. The profound ethical issues raised call for informed, dispassionate debate.

Foubister, V. (2000). Gene therapy group adopts stringent rules on financial ties. *American Medical News*: 10-11.

Frankel, M. S. and A. R. Chapman (2001). "GENETIC TECHNOLOGIES: Facing Inheritable Genetic Modifications." *Science* 292(5520): 1303-.

This policy forum approaches the question of inherited genetic modification, not only to eliminate serious medical problems but proceeding into the realm of improving human beings, perhaps to produce distinctly superior humans. They point out that the fertility industry is not regulated at all and because of this socially unacceptable activity could be carried out without anyone even knowing about it. They propose that there be a policy discussion and regulation of these activities.

Hall, S. S. (2002). "HUMAN CLONING: President's Bioethics Council Delivers." *Science* 297(5580): 322-324.

This news report details the stem cell report that proposed a ban on reproductive cloning and a four-year moratorium on research cloning. The sharp divisions within the Council made it possible for its proposals not to be enacted. It is a very good summary.

Jones, S. (2000). *Genetics in Medicine: Real Promises, Unreal Expectations*, Milbank Memorial Fund.

This commissioned report based on meeting of those who purchase health care in the US and Gt. Britain raises doubt about the relevance of genetics as then understood to the delivery of health care. As the summary stated, "the new genetics is no more than another form of high-tech medicine of crucial importance to a few but irrelevant to the many. At present it suffers from too much publicity and too few results." I think that this article by very practical people is important reading and highly relevant to the changed situation as we see it today.

Knoppers, B. and R. Chadwick (1994). "The Human Genome Project: Under and International Ethical Microscope." *Science* 265: 2035-5.

This very brief paper outlines the ethical issues associated with research and care in human genetics. Five principles, autonomy, privacy, justice, equity and quality are discussed, with appropriate references. These same principles operate to ensure ethical use of genetic materials today.

Koerner, B. (2002). "Embryo Police." *Wired* February: 52-57.

This reportorial piece highlights HFEA, Britain's Human Fertilization and Embryology Authority, which is responsible for regulating what is permissible to do with reproductive tissues and monitoring the field. The author reviews all the kinds of research that could result in a variety of experiments, including those leading to human-other chimeras. The conclusion is that all nations will have to regulate reproductive science and practice intensely.

Kulynych, J. K., David (2002). "Use and Disclosure of Health Information in Genetic Research: Weigh in the Impact of the New Federal Medical Privacy Rule." *American Journal of Law and Medicine* 28(2, 3): 309-324.

This careful paper details the changes in definitions and outlines the rules associated with the HIPAA act, which had not been operationalized at that time.

Lanza, R., J. Cibelli, et al. (2001). "The ethical reasons for stem cell research." *Science* 292(5520): 1299.

This letter to the editor supports stem cell research in the face of political opposition. They make three ethical points. 1) unregulated private organizations will supplant the government in doing this research without the appropriate controls and ethical guidelines 2) embryos will be destroyed in the same numbers 3) the negative viewpoint is limited to a small minority of Americans who shouldn't be allowed to dictate policy.

Magnus, D. and M. K. Cho (2005). "ETHICS: Issues in Oocyte Donation for Stem Cell Research." *Science* 308(5729): 1747-1748.

Malakoff, D. (2003). "Human cloning. New players, same debate in Congress." *Science* 299(5608): 799.

This brief news report describes the Congressional debate surrounding a four year ban on all therapeutic stem cell research as suggested by the President's Commission. While the tide seems to have turned, this gives the players and the arguments.

Marshall, E. (1999). "GENETIC TESTING: Beryllium Screening Raises Ethical Issues." *Science* 285(5425): 178b-179.

This report discusses the use of genetic screening to deny certain jobs encountering beryllium exposure by the Department of Energy because of a demonstrated genetic susceptibility to berylliosis, a severely debilitating and lethal pneumoconiosis. It focuses on an existing practice but the ethical issue in considering genetic screening as consideration for certain lines of work runs counter to public policies insisting that discrimination on the basis of a disability is illegal and immoral. We have learned to accept these protections in relation to college and professional school admission and most employment. Is the beryllium case the camel's nose in the tent? Very worthwhile reading.

Marshall, E. (2000). "BIOMEDICINE: Gene Therapy on Trial." *Science* 288(5468): 951-957.

This news article reviews the Jesse Gelsinger case before all the data were in and interviews a number of people in the gene therapy field as well as detailing the corporate connections of the gene therapy establishment. A most interesting quote was obtained from Arthur Caplan indicating that Wilson did not have a conflict of interest.

Marshall, E. (2002). "Clinical research. Gene therapy a suspect in leukemia-like disease." *Science* 298(5591): 34-5.

This news report describes the situation involving the first leukemia patient who developed leukemia in the course of a gene therapy trial to treat combined immunodeficiency disease.

Marshall, E. (2003). "GENE THERAPY: Second Child in French Trial Is Found to Have Leukemia." *Science* 299(5605): 320-.

With the development of leukemia in a second child in the French combined immunodeficiency trial, gene therapy studies in humans ground to a halt except for a few cancer studies.

McCabe, L. (1996). "Efficacy of a targeted genetic screening program for adolescents." *Am J Hum Genet.* 59(4): 762-3.

The author discusses an article on genetic screening in which a population of school children was invited to be tested for beta-thalassemia or Tay Sachs heterozygosity depending on their backgrounds. Both parent and child had to sign informed consents after a session in which they were taught about the diseases and their inheritance. The article points out that studies such as this might give pause to those who consider the risk of genetic testing to be greater than possible benefits. A persuasive argument for genetic testing for specific conditions is given.

Lebacqz, K, Mendiola, M., T. Peters, et al. (1999). "Research with human embryonic stem cells: ethical considerations. By Geron Ethics Advisory Board." *Hastings Center Report* 29(2): 31-6.

Geron was successful in developing immortalized human embryonic stem cells and convened an ethics advisory board to delineate appropriate ethical practices. They consisted of six points that are elaborated in this document. Paraphrased, they state that 1) the blastocyst must be treated with appropriate respect; 2) Those donating embryos should give full and informed consent; 3) no reproductive cloning; 4) acquisition or development of the feeder layers should not violate norms for human or animal research; 5) such research should be done with concern for global justice; 6) such research should be approved by an independent ethics advisory board in addition to an IRB. These considerations were core to the conclusions of the National Academy of Sciences Committee and have been applied to the regulations of the California Institute for Regenerative Medicine. This is a very worthwhile read.

Merz, J. F. (1999). "Disease Gene Patents: Overcoming Unethical Constraints on Clinical Laboratory Medicine." *Clin Chem* 45(3): 324-330.

Those who control patents on genes that relate to specific disorders or susceptibilities are maintaining monopolies over genetic testing for those genes. This results in diminished availability of the tests and monopoly prices. This interferes with the ability of physicians to diagnose and treat their patients. Unless the patent office requires compulsory licensing of genetic patents that it grants, this situation could become much worse as noted by the American Association for Clinical Chemistry in 1999. This is balanced by the need to maintain very high testing standards for complex assays. I do not believe that much progress has been made to make testing more available or cheaper.

Morella, C. A. (2001). "Stem Cell Research Needs United Support." *Science* 293(5527): 47b-.

This letter by Congresswoman Morella indicated that the scientific community would have to unite and lobby hard to get their views on stem cell research heard and listened to.

Motulsky, A. G. (1999). "If I had a gene test, what would I have and who would I tell?" *Lancet* 354(suppl I): 35-37.

This brief paper by one of the leaders in genetics over the twentieth century asks a series of critical questions about genetic screening. He points out, for example that testing for something for which there is no treatment or effective preventive seems inappropriate. He also notes that non-genetic tests for susceptibilities are sometimes more effective in that many genes could produce the same adverse physiological state. While it doesn't deal directly with research ethics, it is worth our attention.

Noguchi, P. (2003). "Risks and benefits of gene therapy." *N Engl J Med* 348(3): 193-4.

The author, from the FDA, reviews leukemia, the serious adverse event associated with gene therapy for combined immunodeficiency disease, a lethal genetic disorder of the immune system. After a special committee review the study was limited to patients failing bone marrow transplantation, but with the subsequent identification of more cases the trial was stopped completely. This paper gives the arguments for continuing the study in a limited way.

Nowlan, W. (2002). "HUMAN GENETICS: A Rational View of Insurance and Genetic Discrimination." *Science* 297(5579): 195-196.

The author, an insurance executive, give arguments to reassure the body politic that insurance companies are motivated to insure people not to deny them insurance. They further should have the right to charge in accordance with the appropriate actuarial risk. His most cogent argument is that insurers can't insure on the basis of genetic tests that will not lead to a disease for years. Since most individual health insurance policies last only a few years, the companies have little motivation to deny coverage unless there is established illness. He indicated that states have enacted numerous anti-discrimination laws, and that he believes that these are counterproductive. This "other view" is well worth reading because no matter what the future may bring, there is little evidence of insurance discrimination to date.

Okie, S. (2005). "Stem-Cell Research -- Signposts and Roadblocks." *N Engl J Med* 353(1): 1-5.

Parens, E. and E. Juengst (2001). "Inadvertently Crossing the Germ Line." *Science* 292(5516): 397-.

This editorial reflects on the successful pregnancies resulting from transfer of ooplasm from donors to eggs of women whose infertility was due to ooplasmic defects. This process resulted in mitochondria and mitochondrial DNA being transferred. The authors worry about the lack of controls over non-federally funded inherited genetic modifications.

Reich, J. G. (2002). "EMBRYONIC STEM CELLS: The Debate in Germany." *Science* 296(5566): 265-.

Robinson, G. E. (2004). "GENOMICS: Beyond Nature and Nurture." *Science* 304(5669): 397-399.

Rothenberg, KH, Terry, SF. (2002) Before it's too late – Addressing Fear of Genetic Information. *Science*, 297:196-7.

The fears of uninsurability and employment discrimination are widespread as the possibility of meaningful genetic screening approaches reality. While a melange of laws have been passed in state legislatures, this national problem needs a uniform national solution they claim

Sade, R. M. (1994). "Issues of social policy and ethics in gene technology." *Methods Find Exp Clin Pharmacol* 16(7): 477-89.

Technical developments in the last ten years have made possible mapping and sequencing of the entire human genome, along with the possibility of treating genetic disorders by manipulating DNA. A variety of issues regarding potential uses and abuses of these technologies have become apparent. They relate to both genetic screening and gene therapy. Problems facing individuals and their families mostly revolve around rights of self-determination and of confidentiality. Health care professionals will need to design optimal systems to provide genetic counseling and to protect confidentiality of DNA data bases. Society and social institutions will need to develop policies and laws that protect the privacy of individuals whose DNA is stored in data banks. Patenting of the results of gene research remains controversial internationally. Moreover, there is concern in many quarters about society's potential abuse of gene technology for eugenic purposes. Gene therapy is now a reality. There is little disagreement on the use of gene therapy to treat genetic diseases in individuals by somatic cell therapy. There is much controversy, however, over the use of germ-line cell therapy. Gene technology has contributed to the growth among a small group of influential people of the Post-Modern Movement, which is strongly antiscience and antitechnology. This movement may pose a long-term threat to future technological advances and should not be ignored. There is much outside of the laboratory that scientists, particularly molecular biologists, can do to assure a secure place for science and technology in our culture.

Sankar, P. and M. Cho (2002). "Genetics. Toward a new vocabulary of human genetic variation." *Science* 298(5597): 1337-8.

This very thoughtful piece deals with genetic variation in ethnic populations that are being discovered at a rapid rate. Do these findings permit one to use the discredited word "race" for closely related populations? Race has been reconceptualized as a social construct separate from genetic background, but is that actually appropriate? The authors suggest that the word race be defined carefully any time it is used in scholarly publications.

Shapiro, H. T. (1999). "Ethical dilemmas and stem cell research." *Science* 285(5436): 2065.

This brief editorial describes societal dilemmas associated with embryonic stem cell research and how the National Bioethics Advisory Commission addressed them. Essentially, they supported the Federal funding of research using of embryonic stem cells under certain conditions.

Szebik, I. and K. Glass (2001). "Ethical issues of human germ-cell therapy: a preparation for public discussion." *Acad Med* 76(1): 32-8.

At this point debate on the transfer of heritable elements to sperm or egg, thus changing the individual's genome had not been discussed very much although scientific progress was dramatic. The authors, in an attempt to stimulate discussion do a philosophical analysis of the arguments. They claim that because germ-cell therapy affects future generations, its moral status differs from that of somatic-cell therapy. They discuss the concepts of "playing God", moving in the direction of "human enhancement" and, of course ending up with new genomes for the future. They indicate that humanity is already subject to many influences that alter the human gene pool including of course abortion and that human activity already produces irreversible changes. Their most cogent point is that discussion is needed.

Temple, L., R. McLeod, et al. (2001). "Essays on science and society. Defining disease in the genomics era." *Science* 293(5531): 807-8.

Vogel, G. (2001). "BIOMEDICAL POLICY: Bush Squeezes Between the Lines on Stem Cells." *Science* 293(5533): 1242-1245.

This thorough news focus article describes in detail the Bush decision regarding the Federal support of stem cell research. It also describes the search for lines that fulfill the requirements announced by the President.

Vogel, G. (2001). "EMBRYO RESEARCH: British Parliament Approves New Rules." *Science* 291(5501): 23a-.

This reporter discusses the overwhelming passage by the British parliament of rules supporting research using embryonic stem cells and somatic cell nuclear transfer.

Vogel, G. (2001). "Stem cell policy. Can adult stem cells suffice?" *Science* 298(5523): 1820-2.

This news report describes the discussion over whether adult stem cells can take the place of embryonic stem cells either in research or in clinical promise. We know that to study development embryonic stem cells are better. Five years later, the data remain out on the relative roles of the two types of cells in therapeutics.

Vogel, G. (2005). "STEM CELLS: Collaborators Split Over Ethics Allegations." *Science* 310(5751): 1100

This news report discusses the beginning of the unraveling of the Huang empire..

Weiss, R. (2002). Resumption of Gene Therapy Urged. *Washington Post*. Washington, D.C.: A17. October 11, 2002,

Weissman, I. (2002). "Stem cells--scientific, medical, and political issues." *N Engl J Med* 146(20): 1576-9.

This stem cell researcher and stem cell research advocate argues that the current embryonic stem cell lines will be inadequate to fulfill the needs for understanding human development. Further, he argues that cell lines developed from discarded embryos from fertility clinics will not be effective in studying specific diseases. He proposes ways to accomplish this while banning reproductive cloning. This is a brief and useful statement that was taken very seriously by the people of the state of California.

Weissman, I. L. (2005). "Medicine: Politic stem cells." *Nature* advanced online publication.

Kennedy, D. (2006). "Editorial Retraction." *Science* 311(5759): 335b-.

This formally retracts the editorial about human stem cell cloning previously published in *Science*.

Normile, D., G. Vogel, et al. (2006). "CLONING: South Korean Team's Remaining Human Stem Cell Claim Demolished." *Science* 311(5758): 156-157.

This news report in *Science* describes in some detail the investigation of Dr. Hwang's research and the conclusion that human stem cell lines did not exist but that the cloning of a dog did take place.

Stem Cells

Lo, B., P. Zettler, et al. (2005). "A New Era in the Ethics of Human Embryonic Stem Cell Research." *Stem Cells* 23(10): 1454-1459.

The authors from UCSF discuss, well in advance of any clinical opportunities, the ethical concerns surrounding the injection of stem cells in a Phase I trial in humans. The issues they consider include updating the scientists on the health profile of the donor -- you would not want to introduce a genetic disease -- and making sure that the subjects understand what the research entails in terms of, among other things, remote risk and lifelong follow up.

<http://stemcells.alphamedpress.org/cgi/content/full/23/10/1454>

Walters, L. (2004). "Human embryonic stem cell research: an intercultural perspective." *Kennedy Inst Ethics J* 14(1): 3-38.

This report reviews positions, formal and informal, adopted by various religions or spokespersons for non-monolithic religions regarding human embryonic stem cell research. It also reviews policies that have been developed in four regions of the world. An excellent compilation.

Pullman, D. and A. Latus (2003). "Clinical trials, genetic add-ons, and the question of benefit-sharing." *The Lancet* 362(9379): 242.

The authors consider whether those contributing genetic material for research that would yields profitable results should receive some benefit from their contribution. They note that groups contributing to

genetic studies can sometimes be expected to benefit and they suggest that individuals should have the same possibility. They propose a way to accomplish this.

Guenin, L. M. (2004). "The morality of unenabled embryo use--arguments that work and arguments that don't." Mayo Clin Proc 79(6): 801-8.

This very thoughtful philosophical piece dissects arguments for and against the use of about to be discarded embryos for the production of lines to carry out research. He comes up with formulation justifying their use for research purposes. This is a really sound paper and well worth reading carefully

Park, S., S. Orkin, et al. (2006). "Reactions to the Hwang Scandal." Science 311(5761): 606-7.

These are 4 thoughtful letters in reaction the Hwang scandal. The Park letter apologizes for Korean science. The Orkin letter discusses the negative impact on stem cell research. The Martin letter criticizes the editors of Science. The Kwok letter emphasizes the importance of protecting whistleblowers.
<http://www.sciencemag.org/cgi/content/full/311/5761/606b>

Dickenson, D. (2004). "CONSENT, COMMODIFICATION AND BENEFIT-SHARING IN GENETIC RESEARCH." Developing World Bioethics 4(2): 109-124.

This is a very thoughtful and interesting paper. It deals with the issues surrounding getting blood or tissue samples for genetic diagnostics. and for the development of treatments for diseases. These include the lack of informadness in the consent process, especially about the potential economic benefits, the commodification of our bodies, which is somewhat distasteful, and the notions of exploitation and bribery in getting samples from developing countries. There is also the question of the meaning of access to the results of the intervention.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1471-8731.2004.00087.x>

Macklin, R. (2003). "Bioethics, Vulnerability, and Protection." Bioethics 17(5-6): 472-486.

The author deals with vulnerable populations, exploitation, and harm, which are independent variables. She defines exploitation as occurring when the wealthy or powerful take advantage of the poverty powerlessness or dependency of others to serve their purposes. She points out that people can be harmed even if not exploited in clinical research.

<http://www.blackwell-synergy.com/doi/abs/10.1111/1467-8519.00362>

8: Malfeasance and Misconduct

A. Definitions

The definition of Research Misconduct has been debated for at least a decade and the Federal Government has just completed the final rule. It includes not only the definitions of research misconduct but also the regulations by which institutions must address allegations of misconduct as they apply to research in which PHS funds either support the institution or the research. The following is taken directly from the Federal Register:

Sec. 93.103 Research misconduct.

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(a) Fabrication is making up data or results and recording or reporting them.

(b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

(c) Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

(d) Research misconduct does not include honest error or differences of opinion.

Sec. 93.104 Requirements for findings of research misconduct.

A finding of research misconduct made under this part requires that--

(a) There be a significant departure from accepted practices of the relevant research community; and

(b) The misconduct be committed intentionally, knowingly, or recklessly; and

(c) The allegation be proven by a preponderance of the evidence.

Sec. 93.105 Time limitations.

(a) Six-year limitation. This part applies only to research misconduct occurring within six years of the date HHS or an institution receives an allegation of research misconduct.

(b) Exceptions to the six-year limitation. Paragraph (a) of this section does not apply in the following instances:

(1) Subsequent use exception. The respondent continues or renews any incident of alleged research misconduct that occurred before the six-year limitation through the citation, republication or other use for the potential benefit of the respondent of the research record that is alleged to have been fabricated, falsified, or plagiarized.

(2) Health or safety of the public exception. If ORI or the institution, following consultation with ORI, determines that the alleged misconduct, if it occurred, would possibly have a substantial adverse effect on the health or safety of the public.

(3) "Grandfather" exception. If HHS or an institution received the allegation of research misconduct before the effective date of this part.

Sec. 93.106 Evidentiary standards.

The following evidentiary standards apply to findings made under this part.

(a) Standard of proof. An institutional or HHS finding of research misconduct must be proved by a preponderance of the evidence.

(b) Burden of proof. (1) The institution or HHS has the burden of proof for making a finding of research misconduct. The destruction, absence of, or respondent's failure to provide research records adequately documenting the questioned research is evidence of research misconduct where the institution or HHS establishes by a preponderance of the evidence that the respondent intentionally, knowingly, or recklessly had research records and destroyed them, had the opportunity to maintain the records but did not do so, or maintained the records and failed to produce them in a timely manner and that the respondent's conduct constitutes a significant departure from accepted practices of the relevant research community.

(2) The respondent has the burden of going forward with and the burden of proving, by a preponderance of the evidence, any and all affirmative defenses raised. In determining whether HHS or the institution has carried the burden of proof imposed by this part, the finder of fact shall give due consideration to admissible, credible evidence of honest error or difference of opinion presented by the respondent.

(3) The respondent has the burden of going forward with and proving by a preponderance of the evidence any mitigating factors that are relevant to a decision to impose administrative actions following a research misconduct proceeding.

Applicability paraphrased from 93.100:

- a. Research misconduct involving PHS support is contrary to the interests of the PHS and the Federal government and to the health and safety of the public, to the integrity of research, and to the conservation of public funds.
- b. The Department of HHS and the institutions that apply for and receive PHS support for research, training, or research-related activities jointly share the responsibility for the integrity of the research process. HHS has the rights of oversight and recipient institutions have an affirmative duty to protect PHS funds from misuse by ensuring the integrity of all PHS-supported work, and primary responsibility for responding to and reporting allegations of research misconduct.

B. Process

Institutions have the responsibility of dealing with allegations of research misconduct in a two-step process. In the inquiry stage the facts are gathered to the extent necessary to determine whether a full-fledged investigation is necessary. The parallel legal step is an indictment by a Grand Jury. In research misconduct, a positive report of an inquiry results in an investigation, comparable to a trial, carried out by an appointed committee. This is a quasi-legal activity, with lawyers present, disclosure rules, requirements for detailed record keeping and a requirement for decisions of guilt or innocence regarding each allegation.

At the initiation of an investigation, the Office of Research Integrity must be notified. The ORI can be helpful in advising the institution so that the investigation will be carried out with precise adherence to the rules. The results of the investigation are reported to the institutional leadership and to the ORI. If a finding of research misconduct is made, (see above for definitions), then the institution and funding agency determine the appropriate sanctions.

The ORI has the authority to review research misconduct investigations as well as the primary data and to suggest a government investigation if warranted.

Sometimes the complainant (the whistleblower) or the respondent (the accused) is not satisfied with the results of the investigation. They can appeal

to the ORI in writing and if deemed warranted, the case can be presented to an administrative law judge for final adjudication. This is a big change in response to great criticism of the appeals carried out by the ORI directly.

C. Whistleblowing

If you perceive a situation or activity that you think constitutes research misconduct, as a scientist and professional you have a responsibility to report it. While that is part of the underlying bargain of accountability that professionals make with society, whistleblowers usually act on the basis of personal hurt or outrage. However, an allegation of research misconduct must be handled as a very serious matter. Therefore, if you are contemplating making an allegation, consider the following, derived from practical suggestions by Chris Gunsalus.

1. Consider it an inquiry rather than an accusation
2. Talk it over with friends
3. Try to figure out whether there is another side to the story
4. Write it down. Focus on the science and the exact details rather than the person
5. Try to develop support from others in the lab
6. Do not illegally examine someone's data

Other things you should consider prior to making an allegation

1. You may not have a right to know what's going on. Is that okay for you?
2. What kind of satisfaction do you want from the inquiry?
3. If it's your boss, you may have to move. Is that okay for you?
4. Is there a way to achieve your goals without going to the "authorities"?
5. Are you prepared for the long haul and for a bad outcome?

Although federal and state legislation and institutional regulation protect whistleblowers, the outcome of the process is often deleterious to their careers and their incomes.

D. Litigation, the new approach to research management

When the tort bar finds a weakness in any of our industries or enterprises, the stakes immediately go up and the costs of paying out or preventing legal liability add substantial burdens. However, this system of management has played a significant role in the protection of citizens against malfeasance, much to the enrichment of the plaintiffs' lawyers involved. In recent years, the clinical research establishment has been subject to litigation and the results have been a great tightening up of subject protections.

Historical - informed consent claims for medical treatment go back to 1914. Now the clinical research enterprise is subject to new legal claims, an increased number and types of defendants, and use of class action suit technique that can multiply the number of claims. Examples include:

- 1. The Gelsinger case:**
 - Defective informed consent and process**
 - Product liability**
 - Fraud - failed to reveal that previous subjects died and that the investigators had serious conflicts of interest.**

Penn settled eventually for a substantial amount of money.

- 2. Robertson vs Oklahoma- Melanoma Vaccine**
 - Consent failures**
 - Trial was negligently run -investigator malpractice**
 - Fraudulent representation of the purposes, risks and benefits**
- 3. Wright vs Hutchinson Clinic -preventing graft failure in bone marrow transplantation. Tried lymphocyte depletion, which didn't work.**

Seattle Times series called it "Uninformed Consent" They claimed that subjects were lured by greedy doctors into trials where they weren't told all the risks. They were applying current consent rules to 20 year old studies.

The legal claims were:

**Defective consent, research malpractice,
Failure to disclose COIs
Failure to report deaths to IRB appropriately
Failed to update consent forms
"breach of the right to be treated with dignity" under due process
clause of the 14th amendment**

The "Hutch" fought it and won in a landmark decision.

This section derived from Mello, Studdert and Brennan: 2003 Ann Int Med; 139:40-45.

Fraud cases can result in punitive damages and really big awards. Lawyers are now suing everyone including:

- The University,**
- The teaching hospital,**
- The PI,**
- The sponsor**
- Top university officials**
- Individual IRB members**
- The hospital's patient advocate (Abiomed)**

The additional defendants make the costs of litigation much higher and favor the plaintiffs. With many individuals in the same study, the conditions are ripe for class-action suits, which provide great rewards to the attorneys.

Impacts of successful litigation:

- More suits are inevitable**
- It has tightened up research on humans - a good thing**
- It may make IRBs super-conservative, which is a bad thing**
- It may make monitoring of research mandatory**
- It may create a spate of rule-making**

E. The Importance of Trust

Research on humans is based on trust that the truth is told about the study. Subjects trust that the institution is fulfilling its responsibilities to the participants.

Subjects trust that those conducting the study have their best interests at the top of their agenda.

They also expect that conflicts of interest are disclosed to them and to others.

If we fail, the consequences could be disastrous to ourselves, to our institutions and to our standing with the public that supports our endeavors.

CASES Chapter 8

Case: Fabrication

In 1984 a faculty member was up for a tenured position in a clinical department. He was a shoo-in having already published over 100 papers in peer-reviewed journals, mostly as first author.

As it turned out, one member of the promotion committee decided to review some of the papers and found that a number of them used the same instead of different control groups. When doubts were expressed to the chair, co-authors were called and they reported that they had never seen the papers and knew nothing about them. It was discovered that there were no notebooks and no animals had been ordered to do the studies. The miscreant broke down and confessed.

1. What is the most cost-effective way to produce research results?
2. Why did this person behave like this?
3. Could this happen today?
4. Could you believe the co-authors?

Case: Data Falsification

CAST	
<u>Patricia Frankel</u>	<u>Professor and department chair</u>
George Frankel	Patricia's husband, businessman
Edward Milani	Associate Professor, in same department
Jennie Foster	Graduate student in Milani's laboratory
Jim Liu	Assistant Prof at Yale, former post-doc of Milani's
Jeremy Stoessel	Dean

Narrator: Patricia Frankel is a harried department chair, scrambling for talent and trying to keep her own laboratory afloat in the face of ferocious competition. She is having a quiet dinner out with her husband, George, a businessman.

Patricia: Today, Jennie Foster, one of Edward's (Milani, Associate Professor) graduate students, pulled me aside after a seminar. She told me that she had been unable to duplicate the critical purification of an alkaloid regulator of signal transduction that Jim Liu, the post-doc had discovered last year before he went to Yale. The published paper did not contain all the necessary technical data. Jennie figured that she was lucky to be able to go to the lab's original notebooks.

George: The importance of good laboratory documentation.

Patricia: But that's the problem. Jennie said that the notebooks were not helpful. In fact, she said there were many erasures in the dataset, the procedural details were vague and it wasn't proven that they really had pure regulator. Jennie said that when she called Jim at Yale for help, he was friendly and offered to look up his personal notes and get back to her in a week. She said that when she related the conversation to Ed Milano, he said he didn't know the details well enough to help her directly, but he was going to take the notebooks home for review. He would get back to her. That was three weeks ago and she didn't hear from either of them. She saw Ed almost every day.

George: What did you say to her?

Patricia: I told her to be patient. But there's something funny going on here. Why did Ed take the notebooks home? Why would Jim have personal notes? I wonder whether the data in the notebooks supported the conclusions in the paper, which caused quite a stir when it was published.

George: No matter. It's not your responsibility to pursue every suspicious statement or puzzling action that goes on in your department.

Patricia: Well, it's not so simple. As scientists we have responsibility for the integrity of the research record and that means uncovering misconduct. Jennie told me that she made copies of the relevant notebook pages to study and volunteered to show them to me. I wonder whether I should look at them.

George: Well, you know I like Ed. Hasn't he been a productive researcher and inspired teacher? It's hard to believe that he participated in anything dishonest. Maybe Jennie, in her naiveté has it all wrong.

Patricia: That's the dilemma. The suspicion here is of data falsification, a most serious form of research misconduct. Perhaps Jennie was completely off base but she's not naive—in fact, she's really smart. She isn't pointing a finger, yet what she's saying is quite serious.

Patricia: I wonder how to discuss this with Ed. Should I request his notebooks? Should I take this to the dean? I really could use some advice because reporting to the dean will probably initiate an official inquiry.

George: You should think about the potential consequences to you and to Jennie. This could get out of control. Maybe a colleague can help.

Questions:

1. As a colleague of Dr. Frankel's what would you suggest?
2. Did Jennie make an allegation on misconduct?
3. **Is the proposed crime the process of research or the possibility of a false outcome?**

Narrator: Professor Frankel meets with Prof. Milani

Professor Frankel: I hear that there is some problem replicating the purification of your transduction factor.

Professor Milani: Don't worry about it. There is nothing to it. Don't get involved. Leave it entirely to me and I will clear it up. I am reviewing the notebooks and will get back to you soon.

Narrator: After a month without progress, Prof. Frankel takes the problem to Dean Jeremy Stoessel.

Prof. Frankel: Jeremy, we have this little matter that may or may not involve research misconduct. I am puzzled as to what to do because Ed is my friend and the grad student is pretty new but the lack of willingness to communicate led me to take it to you.

Dean Stoessel: Well, this is a serious matter and we can't just let it go by. These things have a tendency to have lives of their own. I am going to have to call for a formal inquiry. Both you and Ms. Foster have to submit written statements to me within 48 hours and be prepared to testify before the inquiry board.

Questions:

1. Prof Milani refused to cooperate with Prof. Frankel, precipitating the inquiry. What is his responsibility here and can this be held against him?
2. How much discretion does the integrity officer, the dean in this case, have when approached with this kind of allegation?
3. Should Prof. Frankel be required to tell Milani that she is going to the Dean?

Narrator: The meeting with Jennie.

Prof. Frankel: Dean Stoessel requested that you and I write a statement describing the problem with Dr. Milani's work. He felt that he had to convene an inquiry to

determine whether there was enough here to result in a formal research misconduct investigation.

Jennie: Why did you go to the Dean without telling me first? I really don't want to do this. It will seem as though I am a whistleblower, which was never my intention. I am really into research and this is likely to ruin my career.

Prof. Frankel: It's too late. The cat is out of the bag. Besides, being a whistleblower will protect your fellowship. You must do this.

Narrator: Jennie was asked to leave Prof Milani's lab and the only other lab that would accept her was Prof. Frankel's. She was shunned by the other graduate students, began to lose sleep and ability to concentrate. At his point she was worried that she had gotten it all wrong and was ruining not only her own career, but those of Prof Milani whom she liked and Jim Liu whom she never met. And for what!

Questions:

1. For what indeed?
1. Does Jennie have any culpability here?
3. Should she have received counseling? When and what kind?
4. Does removal from lab constitute retaliation against a whistleblower?

Narrator:

The inquiry panel impounded all of the relevant laboratory notebooks. It tried to get Jim Liu's personal notes but he denied their existence. With the help of an expert from another university, the panel decided that the combination of the paper and the laboratory notes were not sufficient to allow anyone to prepare the regulator in question. They could not determine whether the purification had indeed been accomplished. The experimental notes had been altered in a suspicious manner. They recommended a full investigation.

Dean Stoessel was concerned that the inquiry panel was too eager to suggest misconduct in what to him seemed to be sloppy science, that was facing validation in other laboratories. Couldn't Ed Milani just repurify the transduction regulator, define the conditions and make the whole problem disappear? However, the report of the inquiry board constrained him to notify the Office of Research Integrity and initiate a full-blown investigation.

Questions:

1. What are Dean Stoessel's degrees of freedom in this case?
 - a. Can he ignore the committee?
 - b. Can he defer or delay action?
2. How should the proposed investigation committee be organized?

1. expertise
2. lawyers

Narrator:

When notified of the impending investigation, Professor Milani initiated legal action for defamation of character and named Jennie Foster, Patricia Frankel and the University.

Ms. Foster, unprotected by the University, refused to testify further and under the advice of her attorney, attempted to withdraw her statement, which, she said, was made under duress.

Professor Frankel carried on her duties gamely but she knew that feelings in her department supporting Professor Milani ran high. Why, they remonstrated, was she so ready to accuse a longstanding and productive colleague? She felt her chairmanship slipping away. She used her influence to get Ms. Foster a training position at the NIH, but Jennie, discouraged, was beginning to think about other career possibilities.

Question:

1. How can society provide adequate protection for righteous whistleblowers without providing excessive protection that would allow chronic malcontents to harass their bosses?

Narrator:

The investigation committee petitioned Yale to request all notes and notebooks that Jim Liu took with him when he left. The Dean at Yale approached Jim but he claimed to have taken nothing whatsoever with him. When asked whether he could prepare a batch of transduction regulator to demonstrate the validity of the process, Jim stated that he did nothing wrong and had no interest in having his career sidetracked, even temporarily. Professor Milani refused to try to prepare a new batch of regulator for testing because, he claimed, the allegation was frivolous.

He told the investigation committee that there was no intended deception and that even if the preparation could not be duplicated, the prepared batch was good and the paper remained well accepted.

Of course, by this time the investigation had gotten out to the scientific public. Professor Milani's lab was being shunned by potential graduate students, as were other laboratories in the department, which was now considered to be "troubled."

The editors of the journal in which the paper was published were disturbed that an investigation was under way.

The ORI listed Professor Milani's case among the investigations it was monitoring.

Question:

1. What do you think about the refusal of Milani and Liu to attempt to prepare a new batch of regulator and define the procedure?

Narrator:

The investigation panel considered three questions, whether the notebooks validated the paper, whether the result was correct and whether there was a pattern of deception either prior to publication or after the allegation of misconduct was aired. After much sifting of evidence they concluded that actual evidence of misconduct was too limited to warrant a positive conclusion. They believed that the data in the notebooks were not adequate to support the results in the paper or permit replication but that the reported experiments had been carried out. They believed that the attitudes of both Jim Liu and Edward Milani were reprehensible in not helping to resolve the issue, and suggested that the journal publish a statement shedding doubt on Liu and Milani's paper.

Questions:

1. What are the risks and benefits of the journal publishing a comment on the paper?

2. At this point what is dean Stoessel's responsibility?

3. The newspapers have been reporting on the case. What are the institution's obligations toward the press and the principals?

Narrator:

At the conclusion of the investigation Professor Milani demands a University statement exonerating him and Jim Liu, a letter of apology for the accusation, and removal of Professor Frankel from her administrative duties. Jennie Foster, learning that the suit against her was not dropped, sends the NIH office of the Inspector General her copies of the notes, suggests a cover-up and requests a full investigation. The IG requests the entire file for re-examination.

Questions:

1. What lessons are there to be learned here?

2. Was science served in this case?

Case – Expropriation of trainees work

A graduate student wrote a thesis detailing a new method for teaching nutrition to schoolchildren. She claimed that one of her thesis advisors appropriated her ideas, began lecturing on her work and eventually got a grant to carry out her proposal, excluding her. All agree that he did that, using it to teach obese adults rather than school children.

She complained, got her Ph.D. but her university did not protect her. The complaint to the ORI at the Department of HHS was examined and dismissed eventually because it did not involve the quality of the scientific record and did not violate the misconduct trio of Fabrication, Falsification or Plagiarism. The faculty member had not plagiarized because he admitted his source, indicating that the thesis was published and thus was in the public domain. The thesis was only available in the institutional library and was not in a peer-reviewed journal.

Questions: 1. What rights does an entrepreneurial faculty member have over the work of a trainee?

2. If you suspected that this was going to happen to you what would or could you do?

3. What protections do trainees need?

Case: Possible Misconduct

As the university ombudsperson you find yourself meeting with Al Gianni a distinguished faculty member who appears somewhat distraught. He explains his predicament as follows:

“About three months ago I fired a post-doctoral fellow for chronic absence and lateness and for trying to get others to do her work. The remainder of the lab

had brought her failings to my attention and with regret I let her go. She promptly found a comparable position in another lab in a nearby research building.

As part of a new paper I recently started writing up a series of experiments she carried out on samples from a clinical trial. Both the statistician and I independently found that the data were tampered with. She altered the computer print outs and enhanced the information in the database so that the results became highly significant instead of indeterminate. We checked this over and over and we are sure she falsified the data. The studies had been completed before we began the process of firing her. I am glad we found it before publication and can prevent it from ever seeing the light of day.

I am worried that she could do this again in current and future positions and contaminate the scientific literature. I really don't know how to proceed and thought I'd see you right away to help me out.

- Questions:
1. What would you ask Dr. Gianni?
 2. What would you tell him about his responsibilities?
 3. Would you give him advice? If, so what advice?

Case: Unsatisfactory Study

A large drug company identified a series of small molecules that stimulated the release of growth hormone leading to the increased production of the anabolic hormone IGF₁, which normally declines profoundly with aging. It decided to conduct trials in elderly physically disabled people with low IGF₁ levels to increase the circulating IGF₁, and thus produce the beneficial effects of GH therapy, but using a single pill a day. If there were beneficial effects, they could thus be achieved inexpensively. Extensive animal trials showed enhanced GH secretion without perceived adverse effects. Phase I and phase II trials were quite successful in that there were no short-term ill effects and the drug reliably increased IGF₁ levels in a dose-dependent manner.

The phase III trial was double blinded and involved 35 centers. The participant population was that of partially disabled persons over the age of 65. Most of them were over 75. (65 is considered young these days). In addition to several blood collections, utilizing a machine that gave objective recordings of power and load, numerous measures of muscle strength were taken every two months in a six-month trial. During the conduct of the study the clinical trials coordinators saw that some of the participants experienced functional improvements but that was not seen in the muscle strength testing. One man stopped using a cane, for example and several others improved their ambulation significantly. About four months into the study, a few participants developed overt hyperglycemia while a few others experienced a decrease of glucose sensitivity.

The company stopped the study at six months and has denied numerous entreaties by the investigators to analyze and publish it. The investigators do not have access to the data. It is rumored that the company gave up research into the whole category of compounds.

Recent studies of GH administration to the elderly have shown deterioration of glucose tolerance and some instances of overt diabetes. GH is being utilized at an increasing rate in the care of older persons who can afford its costs, even though it is not approved for that purpose and insurance companies will not pay for it.

Questions:

- 1. What are the issues raised by this case?**
- 2. Is there research misconduct here?**
- 3. Would there be different issues if the drug had been FDA approved and the trial was a Phase IV trial.**
- 4. How would society best be served?**

Bibliography

(2004). Clinical Trials on Trial. The Wall Street Journal. New York. March 3, 2004

Kennedy, D. (2006). "Editorial Retraction." Science 311(5759): 335b-.

This formally retracts the editorial about human stem cell cloning previously published in Science.

Normile, D., G. Vogel, et al. (2006). "CLONING: South Korean Team's Remaining Human Stem Cell Claim Demolished." Science 311(5758): 156-157.

This news report in Science describes in some detail the investigation of Dr. Hwang's research and the conclusion that human stem cell lines did not exist but that the cloning of a dog did take place.

Agres, T. (2002). "Science on the Sly: Guilty plea in Cleveland Clinic case becomes latest example of theft from research labs." The Scientist Summer: 16-18.

This unusual case involves the stealing and transfer of scientific materials from one lab to another and then out of the country. The perpetrator was accused of economic espionage, altering and destroying trade secrets, and interstate and international transfer of stolen materials. This case underscores the increasing value of research materials and the need for security even in academic labs. The irony is that these materials could have been shared under a material transfer agreement.

Baltimore, D. (1993). "Shattuck Lecture--Misconduct in Medical Research." N Engl J Med 329(10): 732-3.

Barinaga, M. and J. Kaiser (1999). "MISCONDUCT: Fraud Finding Triggers Payback Demand." Science 285(5431): 1189a-1190.

This news report indicates that the National Cancer Institute asked the Lawrence Berkeley national labs for a return of \$800,000 in research funds when they exposed allegedly fraudulent research by a colleague. The work had put electromagnetic fields in play as influencing cellular function. The lab agreed to return unspent money but not the whole grant.

Brody, J. (2004). A Top Scientist's Research is Under Attack. The New York Times. New York, NY. May 6.

A major nutrition investigator's work was published then seriously challenged as being statistically invalid. The investigator was supporting the use of a vitamin preparation that he designed for cognitive maintenance and licensed to his daughter's company. He left Canada and moved to India after the news broke.

Dayton, L. (2002). "Scientific misconduct. Hall probe continues; no 'willful' fraud." Science 296(5568): 641.

This report of an Australian case in which allegations of willful conducting scientific fraud were lodged against a prominent clinical investigator. Although he was reprimanded and asked to do some restitution, he was not judged to have committed research misconduct pending a second investigation. A lesson for those who run laboratories.

Ding, Y. (2002). "SCIENTIFIC MISCONDUCT: Beijing U. Issues First-Ever Rules." Science 296(5567): 448-.

These parallel western rules regarding research.

Enserink, M. (2003). "NEUROSCIENCE: Singapore Trial Halted, British Scientist Fired." Science 300(5617): 233a-.

The PI, a well known neurologist was found to have misled subjects as to the research protocol and provided an inadequate consent. He also obtained the names of potential subjects and called them directly, violating their privacy rights.

Fitzgerald, M. H. (2004). "Big Basket or Mission Creep?" Professional Ethics Report 17(2).

Grinnell, F. (1999). "Ambiguity, trust, and the responsible conduct of research." Sci Eng Ethics 5(2): 205-14.

Ambiguity associated with everyday practice of science has made it difficult to reach a consensus on how to define misconduct in science. This essay outlines some of the important ambiguities of practice such as distinguishing data from noise, deciding whether results falsify a hypothesis, and converting research into research publications. The problem of ambiguity is further compounded by the prior intellectual commitments inherent in choosing problems and in dealing with the skepticism of one's colleagues. In preparing a draft code of ethics for the American Society of Biochemistry and Molecular Biology (ASBMB), an attempt was made to take into account the ambiguities of practice. Also, the draft code adopted trust as its leading principle, specifically the importance of trust as a condition necessary for there to be science. During revision of the code, the focus on trust was changed. The new orientation was on trust as a consequence of carrying out science responsibly. By addressing the obligations necessary to engender trust, the ASBMB ethics code not only sets professional standards, but also makes a clear statement of public accountability.

Gunsalus, C. K. (1998). "How to Blow the Whistle and Still Have a Career Afterwards." Sci Eng Ethics 4(1): 51-64.

This paper is must reading for everyone entering science and teaching. The author uses her vast experience to report the necessity of whistle blowing and the difficult road that whistleblowers may tread despite much legal protection. She carefully teaches how to be an effective whistleblower, something that every member of a research team should read.

Guterman, L. P., W. (2003). Former Graduate Student Sentenced to Prison for Faking Theft of Research. Chronicle of Higher Education, August 21.

Here's a good one. A graduate student who had done no work for several years (good mentoring here) just reported all his notebooks stolen. He was quickly caught and jailed for 10 months for theft. (The notebooks didn't belong to him.)

Gwynne, P. (1999). "Corporate Collaborations." *The Scientist* 13(11): 1, 6.

Hagmann, M. (1999). "SCIENTIFIC MISCONDUCT: Researcher Rebuked for 20-Year-Old Misdeed." *Science* 286(5448): 2249a-2250.

The seamy history of the availability of human growth hormone for Genentech to develop was elucidated when Peter Seeberg admitted to taking samples from his UCSF lab when he moved to Genentech and not indicating the source in a major subsequent paper. Subsequently Genentech built UCSF magnificent laboratories in payment for the stolen materials.

Hagmann, M. (2000). "SCIENTIFIC MISCONDUCT: Panel Finds Scores of Suspect Papers in German Fraud Probe." *Science* 288(5474): 2106-2107.

This news report characterizes the extent of fraudulent papers turned out by a German oncologist. The suspect papers were in numerous journals and will take years to recover from. They involved 52 papers and 357 apparent manipulations.

Healy, B. (1993). "Sounding Board: The Dingell Hearings on Scientific Misconduct." *N Engl J Med* 329(10): 725-7.

Dr. Healy, Secretary of HHS responds to congressional accusations against the ORI and NIH. It's good reading.

Hoeksema, H. L., J. Troost, et al. (2000). "Fraud in a pharmaceutical trial." *The Lancet* 356(9243): 1773.

The report illustrates how the Dutch handled a case of clinical research misconduct in which they reconstructed the data and determined that the investigator had surely fabricated the submitted data and sent mixed blood from a few persons rather than individual draws to the core lab. A useful example of quiet competent pursuit of the question.

Horton, R. (1999). "Scientific misconduct: exaggerated fear but still real and requiring a proportionate response." *The Lancet* 354(9172): 7.

This editorial discusses national committees to deal with allegations of scientific misconduct. He mentions pressures to more effectively regulate research. However, others decry the dead hand or regulators inhibiting research. These questions are still with us.

Hotz, R. L. (2003). Medical Tests Skewed, Study Finds. Commercial ties are the outcome of research at universities, Yale investigators say. *Los Angeles Times*. Los Angeles. January 22, 2003.

A very nice brief summary of the problem of institutional Conflict of Interests and the potential consequences.

Office of Research Integrity. (1999). *Scientific Misconduct Investigations: 1993-1997*. Department of Health and Human Services.

This provides a statistical analysis ORI materials relating to investigations. They have a new one that is a lot better.

Jacobson, P. D. and S. D. Pomfret (2000). "ERISA Litigation and Physician Autonomy." *JAMA* 283(7): 921-926.

The Employee Retirement Income Security Act (ERISA), enacted in 1974 to regulate pension and health benefit plans, is a complex statute that dominates the managed care environment. Physicians must understand ERISA's role in the relationship between themselves and managed care organizations (MCOs), including how it can influence clinical decision making and physician autonomy. This article describes ERISA's central provisions and how ERISA influences health care delivery in MCOs. We analyze ERISA litigation trends in 4 areas: professional liability, utilization management, state legislative initiatives, and compensation arrangements. This analysis demonstrates how courts have interpreted ERISA to limit physician autonomy and subordinate clinical decision making to MCOs' cost containment decisions.

Physicians should support efforts to amend ERISA, thus allowing greater state regulatory oversight of MCOs and permitting courts to hold MCOs accountable for their role in medical decision making.

Johnson, W. B. and N. Nelson (1999). Mentor-Protégé Relationships in Graduate Training: Some Ethical Concerns. *Ethics & Behavior*. 9: 189-210.

The authors, dealing with psychology graduate students analyze the mentor-mentee relationship and define the characteristics of an appropriate mentor. They indicate that mentoring involves a number of ethical dilemmas. In this article, they deal with competence to mentor, equal access to mentoring, exploitation in mentoring relationships, and multiple role demands related to mentoring as well as describing to the mentee the nature of the mentoring relationship. They conclude with recommendations for both mentor and mentee.

Kaiser, J. (1999). "POLICING OF SCIENCE: A Misconduct Definition That Finally Sticks?" *Science* 286(5439): 391a-.

This news report details the final version of definitions of research misconduct.

Kaiser, J. (1999). "SCIENTIFIC MISCONDUCT: Shalala Takes Watchdog Office Out of the Hunt." *Science* 286(5441): 883a-.

This news story documents the downgrading of the Office of Research Integrity by taking away its investigative powers and making it primarily an educational agency.

Kaiser, J. (2004). "PATIENT RECORDS: Privacy Rule Creates Bottleneck for U.S. Biomedical Researchers." *Science* 305(5681): 168-169.

Kennedy, D. (2002). "More Questions About Research Misconduct." *Science* 297(5578): 13-.

Kennedy, D. (2002). "Not Wicked, Perhaps, but Tacky." *Science* 297(5585): 1237-.

An introduction to research malfeasance that falls short of "misconduct" but is much more prevalent. Do we really have to do these things?

Kuznik, F. (1998). "Medical Whistle-Blowers." *Hippocrates* October: 39-47.

This is a very useful article detailing the stories of a number of whistleblowers in cases of medical care and research. It validates the point that as a group they do poorly careerwise but their consciences gave them no choice but to seek the truth.

Malakoff, D. (2000). "CLINICAL RESEARCH: Flawed Cancer Study Leads to Shake-Up at University of Oklahoma." *Science* 289(5480): 706-707.

This news report details the changes in clinical research oversight initiated at the Univ. of Oklahoma in response to findings of terrible sloppiness in carrying out studies. A major vaccine study for cancer was stopped. This was one of the first examples of institutions needing to clean up their research management.

Malakoff, D. (2002). "Student Charged with Possessing Anthrax." *Science* 297(5582): 751-2.

This little news report probably warned everyone who possesses controlled biological agents to follow the law, register the agents and keep them under tight lock and key. Institutions also have to monitor their inventories of these substances and deal very carefully with their transfer.

Malakoff, D. (2003). "SCIENTIFIC MISCONDUCT: The Multiple Repercussions of a Fudged Grant Application." *Science* 300(5616): 40-.

This news report describes the consequences of fudging preliminary work on a research grant and being caught. The allegation from an administrative assistant provoked an investigation and an admission of guilt. The grant still got funded but the investigator was no longer in charge of the program. Beware.

Mariner, W. K. (2000). "What Recourse? -- Liability for Managed-Care Decisions and the Employee Retirement Income Security Act." *N Engl J Med* 343(8): 592-596.

Marshall, E. (1995). "Suit Alleges Misuse of Peer Review." *Science* 270(5244): 1912-4.

When the money is substantial the temptation to use the information that you are supposed to keep confidential may become overwhelming. Be careful, however, you may be sued. An instructive case.

Marshall, E. (1999). "SCIENTIFIC ETHICS: Two Former Grad Students Sue Over Alleged Misuse of Ideas." *Science* 284(5414): 562-563.

This news report deals with allegations that Pis took graduate student's ideas and used them for their own grants. What the investigator did was surely bad manners and perhaps worse but it was not considered to be research misconduct. Could it have been violation of fiduciary responsibility to a mentee? This again emphasizes the unknowns in the relationship between investigators and trainees.

Marshall, E. (2000). "SCIENTIFIC MISCONDUCT: How Prevalent Is Fraud? That's a Million-Dollar Question." *Science* 290(5497): 1662-1663.

This news article reviews estimated misconduct frequency in research. The most striking finding was that one half of students were willing to fake data to get ahead. Investigators claim to know of instances of misconduct, but that has to be taken with a grain of salt.

Marshall, E. (2002). "Cancer Study Lawsuit Dismissed in Oklahoma." *Science* 295(5557): 949-50.

Medical Research Law and Policy Report. (2002). Current Climate Fostering More Misconduct, But Education, Monitoring Can Reduce Risks. Bureau of. National Affairs.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). "The Belmont Report: ethical principles and guidelines for the protection of human subjects of research." US Government Printing Office.

Normile, D. (2004). "RESEARCH ETHICS: South Korean Cloning Team Denies Improprieties." *Science* 304(5673): 945-.

Pascal, C. (1999). "The History and Future of the Office of Research Integrity: Scientific Misconduct and Beyond." *Sci Eng Ethics* 5(2): 183-198.

The director of the ORI gives his view of the functioning of the agency in the past and the concerns to which they will be directed in the future.

Petersdorf, R. G. (1986). "The Pathogenesis of Fraud in Medical Science." *Ann Int Med* 104(February): 252-254.

Discussion of fraud in medical science has always been with us. Some of the underlying causes were discussed in this paper, which focuses on hypercompetitiveness, and inadequate supervision and oversight.

Rhoades, L. (2004). New Institutional Research Misconduct Activity 1992-2001. O. o. R. Integrity, Department of Health and Human Services.

Rhoades, L. (2004). ORI Closed Investigation into Misconduct Allegations Involving Research Supported by the Public Health Service 1994-2003. O. of. R. Integrity, Department of Health and Human Services.

Stein, R. (2005). Researcher Fabricated Data in Studies on Women. *Washington Post*. March 18, 2005

This famous case of fabrication shocked the establishment because the perpetrator was well known and slated to receive an important award. He had misused about \$11 million and had published fraudulent data. He had to pay back some money and be barred from NIH research support for life.

Steneck, N. (1999). "Confronting misconduct in science in the 1980s and 1990s: what has and has not been accomplished?" *Sci Eng Ethics* 5(2): 161-76.

He details the state of affairs before attention began to be directed at research misconduct, the formation of the ORI and the changing attitudes of investigators and institutions until the time of publication. He deals with confronting misconduct, promoting integrity and ensuring integrity. He points out that ensuring integrity has not been addressed. In the context of today's situation, perhaps we are now finally addressing the latter. I think the lawyers made us do it.

Swazey, J. P., M. S. Anderson, et al. (1993). "Ethical Problems in Academic Research: A survey of doctoral candidates and faculty raises important questions about the ethical environment of graduate education and research." *American Scientist* 81: 542-553.

This study has become a classic because it clearly demonstrated the extent of questionable behavior in both faculty and trainees in a variety of fields of science. It is worthwhile reading – and don't think that your field is any more honorable.

Taubes, G. (1993). "Misconduct: Views from the Trenches." *Science* 261: 1108-11.

This news item describes effective misconduct processes at UCSF, UCSD, Harvard and Univ. of Illinois as well as interviewing some of the responsible persons. The process at UCSF is described in some detail.

Trounson, R. O. et al (2003). Researchers Violated Rules, UCLA Says. *Los Angeles Times*. Los Angeles, CA. April 16, 2003.

This is a tricky one. The investigator arranged to work on data and blood samples obtained from an unapproved study in China without getting permission from his own institution's IRB. He was sanctioned even though he did not participate in the original study.

Woodward, J. and D. Goodstein (1996). "Conduct, Misconduct, and the Structure of Science." *American Scientist* 84(5): 479-91.

This analysis is concerned with the true structure of science as it differs from the homilies that pretend to describe this most complicated of human endeavors. The authors take apart a series of ethical principles used to characterize science and try to demonstrate that, for misconduct the only important thing is whether the scientific record was damaged by falsification or fabrication, results that it takes expertise to detect. They propose that the definition of scientific misconduct be limited to those activities. Much of their view has been adopted, finally in the new definition although plagiarism was not purged as they suggested.

Youngner, J. S. (1998). "The Scientific Misconduct Process: A Scientist's View From the Inside." *JAMA* 279(1): 62-64.

The author analyzes the activities of the Office of Research Integrity as an investigatory body and concludes that the requirement for confronting the purported perpetrator and allowing a defense was only met during the appeal process. The ORI was downgraded not long after this paper and the misconduct review now resides in the institutions and in the Inspector General's office of the Federal granting agencies. Investigations seem to be going much better at this point.

Cho, M. K., G. McGee, et al. (2006). "RESEARCH CONDUCT: Lessons of the Stem Cell Scandal." *Science* 311(5761): 614-615.

This brief Policy Forum reflects on the reasons for the Hwang stem cell scandal. They reflect on the importance of trust in science. They indicate that scientific self-management works best in a questioning flat rather than a hierarchical laboratory environment and that widespread understanding of and buy-in regarding research ethics is required. It was not present in Kova. In my view, the Koreans were acting from a survivalist mentality in their effort to compete with America. In that mental mode, the only thing that counts is success.

<http://www.sciencemag.org/cgi/content/full/311/5761/614>