

## 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**

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

**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](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  $\beta$ -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  $\beta$ -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?

### 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](http://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](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.bmjournals.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.globaethics.bham.ac.uk/consultancy/Retained\\_organ.htm](http://www.globaethics.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.