Principles of ethics

The principles of doing "good" and not doing "harm" are the essence of every code of medical ethics. It is the duty of the medical doctors to their patients to exercise their professional skills in an ethical manner and to observe the laws of the community. The essential purpose is to ensure that patients' trust in the medical profession is deserved. This is achieved by protecting patients and ensuring that they are able to obtain the maximum benefits available from medicine. At the same time, medical ethics aim to protect patients from the abuse that can occur when one person is in a position of power (in this case, based on superior medical knowledge and, often, status) *vis-à-vis* another.

Medical ethics are generally considered to be derived from the teachings of the Greek physician Hippocrates (460–377 BC), commonly known as the Father of Medicine. The ethical principles he taught survive today in the form of an oath (the Hippocratic Oath) traditionally (if not actually) taken by those entering medical practice. While the exact wording has changed to reflect more modern thinking and practice, the essential principle remains the same: the patient's interests are paramount. Codes of ethics have been enriched by the influence of religion and culture. Arabic and Islamic oaths have been developed and are used in medical schools in most of the Eastern Mediterranean Region.

The best known modern version is the Declaration of Geneva, adopted by the World Medical Association (WMA) in 1948 and subsequently amended in 1968, 1983 and 1994 (see Annex 1). The International Code of Medical Ethics of the World Medical Association—1949 was adopted by the WMA at London in October 1949 and has been used as the basis for various codes of ethical practice adopted by different national medical associations (see Annex 2).

In recent times, as an aid to decision-making in medicine and as a starting point for discussions on medical ethics, four principles have been generally agreed as fundamental. These are:

- *Autonomy*
  The right of patients to make decisions on their own behalf.
- *Beneficence*
  The duty or obligation to act in the best interests of the patient.

- *Non-maleficence*
  The duty or obligation to avoid harm to the patient.

- *Justice*
  This embodies concepts of fairness and giving what is rightfully due. It applies not only to the individual but also in the wider medical context and it incorporates notions of equity and fair distribution. This is important when medical services are distributed, as they usually are, in an environment of limited resources. In forensic medicine, justice is the goal that is being pursued.

While concern for safeguarding patients' privacy, as manifest by the duty to maintain confidentiality, can be derived from the first two principles above, some have regarded the concern as so important as to list "privacy" as a fifth principle.

The ethical standards of those working in medical laboratories and forensic medical institutions are derived from medical ethics and other codes and incorporate the same principles. Therefore public expectations of them will reflect, with regard to ethical standards, those expected of the medical profession generally. It is the responsibility of the professionals, whether medically qualified or not, working in those institutions, to ensure that these expectations are realized and that they are worthy of the same level of trust that the medical profession has come to enjoy.

After introducing some concepts common to both areas, we have divided this publication into two parts. This reflects the fact that, while the practice of forensic medicine has many health-related aspects and consequences, there is a duality of purpose: the interests of the patients (in clinical forensic medicine) on the one hand, and the proper administration of justice on the other. Working in this different environment carries with it a different, although allied, set of values and ethics to the patient-oriented service of laboratory medicine.

Definitions

- *Doctor*
  "Doctor" is used in the general sense of "registered medical practitioner". In some parts of the world the term "physician" would normally be used in this way, whereas in other places the term "physician" is restricted to a specialist in internal medicine.
- *Ethical practice*
  Ethical practice can be regarded as good technical practice accompanied by proper attitudes and behaviour. In deciding what is proper, reference is often made to moral values voluntarily adhered to within the community and to standards espoused in various codes of professional practice.
- *Forensic medicine*
  Forensic medicine is the application of the principles and practice of medicine to the proper administration of justice. For the purposes of this document, it includes the discipline of forensic pathology and clinical forensic medicine. In many parts of the world, these two disciplines are practised jointly, in others separately.

1.1 General application of ethical principles

Medical laboratories have responsibilities to others. There are three main groups to whom responsibility is owed:

- *Patients*
  Medical laboratory professionals are accountable for the quality and integrity of the services they provide. This obligation includes maintaining individual competence and endeavouring to protect the patient from incompetent or illegal practices by others.
- *Colleagues and the profession*
  Medical laboratory professionals should strive to uphold the dignity and respect of their professions and maintain a reputation for honesty, integrity and reliability. They should aim to contribute to the advancement of the profession by improving the body of scientific knowledge, promoting high standards of education and practice and collaborating with colleagues and other health professionals where practicable.
- *Society*
  Professionals working in a medical laboratory also have a responsibility to contribute to the general well being of society. This may be within their sphere of professional competence or simply as members of the community.

  Medical professionals should comply with relevant laws and regulations pertaining to their professional activities. The medical profession is committed to a high standard of care and practice, and professionals should endeavour to influence those that do not meet this standard.

1.2 Collection of information

Laboratories must collect sufficient information to identify adequately patients and specimens. They also should collect sufficient information for other legitimate purposes, but unnecessary information should not be collected. If possible, there should be sufficient clinical information to enable the test to be correctly performed and interpreted. Other legitimate purposes may involve information relevant to the safety of other patients and staff as well as information required for billing purposes and resource management, including utilization reviews. The patient should be aware of the information collected and the purpose for which it is collected.

1.3 Collection of specimens

All procedures carried out on competent patients require their informed consent. Where the patient is incompetent by reason, for example, of age or mental state, consent may be given by a parent or other properly authorized person. In exceptional circumstances when this is not possible, necessity may justify the procedure when it is clearly in the best interests of the patient that the procedure be performed. For most routine laboratory procedures, consent can be inferred when a patient presents at a laboratory and willingly submits to the usual collecting procedures, such as venepuncture. However, certain procedures, especially the more invasive procedures (such as bone marrow aspiration), will require a more detailed explanation of their risks prior to consent being given. Some tests, such as certain genetic testing, will require special pre-test counselling to ensure that the patient fully understands the implications of the test result.

Adequate privacy for the patient must be made available. It should be appropriate for the type of specimen (or information) being collected, and the cultural expectations of the patient and the resources available should be borne in mind.

1.4 Performance of tests

All tests must be carried out to an appropriate standard which should be determined in detail by professional organizations or regulatory authorities. Accreditation programmes designed to promote standards and ensure compliance are to be encouraged. Where no such guidance is available the patient's interests will prevail. In some situations, this may mean that a laboratory should refuse to attempt a test rather than produce an unreliable result which could result in harm being done to the patient. All laboratory work must be carried out with the high level of skill and competence expected of the medical, scientific and allied health professions.

1.5 Reporting of results

Test results are confidential unless disclosure is authorized. They will normally be reported to the clinician who requested the tests and may be reported to other parties with the patient's consent or as required by law. Decisions concerning implied consent for the reporting of results to other practitioners involved (such as consultant practitioners to whom the patient has been referred) should be made

carefully taking into account local customs. The laboratory should have written procedures detailing how various requests are to be handled, and this information should be made available to patients on request. The laboratory is also responsible for taking all reasonable precautions to ensure that the method of transmitting results to requesting clinicians, or other authorized persons, is secure and reliable. This applies whether transmission is by courier, public post or electronic means. The laboratory is also responsible for ensuring that the turnaround time for results is reasonable, taking into account the type of test and the patient's condition. There should be the facility to report urgent results as soon as they are available.

In addition to the accurate and timely reporting of test results, the laboratory is also responsible for ensuring that, as far as possible, the results are correctly interpreted and applied in the patient's best interests. Care must be given to the construction and format of the test report so as to facilitate correct interpretation and diagnosis. When appropriate a pathologist or some other competent professional should be available to discuss results. Consultation with regard to the selection and interpretation of tests is part of a medical laboratory service.

1.6 Storage and retention of medical records

The laboratory must ensure that information is stored so that there are reasonable safeguards against loss, unauthorized access, tampering or other misuse. Test results must never be altered or corrected, *except by properly authorized persons in accordance with established procedures*. The retention of medical records may be defined by various statutory requirements, and these need to be considered together with any guidelines issued by relevant professional bodies. Laboratories should develop their own protocols indicating how long different results, specimens and slides will be kept for. Test results should be physically available for ready authorized access. When the time comes for medical records to be destroyed this should be carried out in a way which minimizes the risk of unintentional disclosure.

1.7 Access to medical records

Access to medical laboratory records should normally be available only to the following:

- the clinician requesting the test
- the patient

- laboratory and hospital staff if required for the management of the patient
- other authorized individuals.

Incompetent patients such as children and intellectually impaired individuals have the same right of access as competent adults, although this right may be expressed through a parent or authorized agent. Parents, on the other hand, do not always have *automatic* right of access to their children's medical information, and different countries have different laws and customs in this respect. The laboratory should develop protocols on how to handle different requests taking into account local laws and customs. In exceptional circumstances the withholding of health information from individuals normally authorized to receive it may be justified (the top management of the laboratory would make such a decision). An example of such a circumstance is when disclosure may be contrary to a patient's best interests.

Where a request is made for access to test results by an authorized person the laboratory must first satisfy itself as to the identity of the person making the request. The way in which this is done, and the degree of certainty associated with the process, will vary with different situations.

Different methods may exist in the same laboratory for different tests. For example a degree of certainty associated with the identity of an authorized person seeking an HIV test result may be much greater than that required of one asking for the results of a routine haemoglobin test. Laboratories need to establish appropriate procedures for each situation.

1.8 Financial arrangements and organizational matters

Medical laboratories must be able to function with professional independence. They should not be subject to non-medical control where this has the potential to interfere with their ability to act freely in the best interests of the patient. They may not enter into financial arrangements with referring practitioners or funding agencies where that arrangement acts as an inducement or an impediment for the referral of tests or patients, or interferes with the doctor's independent assessment of what is best for the patient. This assessment, however, will usually be made in an environment of limited resources and so excessive application of these resources to any one individual may not be acceptable, particularly if it results in a failure to deliver a fair share of required services to another individual.

It is desirable that private laboratory collecting rooms be completely separate and independent from the referring practitioner's rooms but where this is not practicable, any financial arrangements must not include any element of inducement.

Laboratories should also be aware of situations which could give rise to conflicts of interest and take particular care. Such situations may arise where pathologists in private practice can self-refer work. Any such self-referred work must be justifiable.

The medical laboratory has a difficult ethical responsibility when operating in an environment of limited resources provided by a third party such as the state. On the one hand there is an obligation to ensure that patients receive all the necessary services to which they are entitled but, on the other hand, there is an obligation to see that resources are not wasted so that other patients are consequentially deprived of their fair share, and the tax payer (or other funding agent) is not unreasonably burdened. The practical implications of this will vary in different situations and particularly from country to country. There will also be different pressures on a laboratory depending upon whether funding is on a "budget" or a "fee-for-service" basis, and the extent to which those resources are under the control of the requesting clinician rather than the laboratory. Nevertheless, there is a responsibility on the laboratory to be involved, to the extent that is reasonable and practicable in the equitable allocation of resources.

1.9 Some special applications

1.9.1 Clinical pathology (clinical chemistry, haematology, microbiology, immunology)

Most of the issues are covered under general principles. As with histopathology and cytology, the results of tests in these areas can have a life-altering impact upon patients. Information provided about the results, and the manner of its provision, must assist the treating doctor to properly advise the patient about the diagnosis and its consequences.

1.9.2 Anatomical pathology

Autopsies[1]

Generally speaking, there are two types of autopsy: the "hospital" autopsy, which requires the voluntary consent of a properly authorized person (often the senior next of kin) and the "forensic", which is autopsy performed at the request or

[1] This section is complementary to Part 2, on forensic pathology, and should be read in conjunction with it.

direction of a coroner or other authority to meet statutory death investigation requirements. This section deals with the former.

An autopsy is the post-mortem examination of a body to provide information of medical or scientific use, including the cause of death, or for other relevant purposes such as the resolution of legal issues. The autopsy is an investigation which can have significant public and private consequences. The latter may be lost if the autopsy is limited to merely establishing the cause of death. The community, including the next of kin, has a right to expect that systems are developed to ensure that all the potential benefits are realized (these benefits are set out in the section on forensic pathology).

It can be difficult for families to cope with issues related to autopsies at the time of bereavement. Hospitals and forensic pathology institutions should have adequate facilities to advise, counsel and support bereaved relatives. Sudden or traumatic circumstances leading to death are particularly recognized as leading to much psychological stress, and the pathologist and other staff should not add to this by insensitivity. The body of the deceased person must at all times be handled with respect, and the relatives must be able to rely on this occurring.

Consent for autopsies

Many religions and cultures do not accept the need for or the desirability of autopsies, and this must be accepted. Procedures relating to consent for autopsies will usually be governed by law and these must be followed meticulously. In most countries, the non-forensic or hospital autopsy requires prior consent from the next of kin. This means that the nature and outcomes of the autopsy must be properly and sensitively explained. This will include an explanation of any need to retain tissues for the purpose of the autopsy or the possibility that tissues may be used for research or teaching purposes. In some cultures the removal of the brain and the heart, particularly if they are retained after the rest of the body is released for burial, is particularly sensitive. The interaction with the next of kin should be conducted in a manner that promotes discussion and encourages them to ask questions. The laboratory should have a clear understanding of the procedures for authorization of an autopsy in the absence of any next of kin or if they cannot be contacted.

1.9.3 Histopathology and cytology

In the course of a histopathological or cytological examination certain observations may be made (such as the presence of spermatozoa) which are not related to the purpose of the examination. Careful thought should be given as to

whether or not such observations should be reported as there could be significant social implications. As in clinical pathology, tissue diagnosis must provide information to assist the treating doctor to properly advise the patient about the diagnosis and its consequences.

1.9.4 Reproductive technology

Issues raised by discussions of reproductive technology may touch on deeply held convictions and religious beliefs, as well as on perceptions about what constitutes a human being or a person, about identity, about the family and about the sense of one's own characteristics living on in some form after death. Just as these convictions and perceptions vary, so does the way different societies and religions treat these issues. Consequently it is not possible to arrive at a universally accepted ethical view on this subject. The different and strongly held views on abortion, artificial insemination by donor, *in vitro* fertilization, gamete intrafallopian transfer, and other procedures and techniques are examples of this concern. Detailed discussion of these important areas is beyond the scope of this document.

1.9.5 Transfusion medicine

The code of ethics for blood donation and transfusion, which was unanimously approved by the general assembly of the International Society of Blood Transfusion during the Society's 16th Congress (Montreal, 16–22 August 1980) is given in Annex 6. The statement on the ethics of voluntary, non-remunerated blood donation of the Third International Colloquium on Recruitment of Voluntary Blood Donors, which was endorsed by the International Group of Red Cross Blood Transfusion Experts, is given in Annex 7.

Voluntary donation

Blood donors should give their blood voluntarily and without expectation of payment. No pressure to donate should be exerted on a potential donor. Volunteer blood donors give blood of their own free will and without coercion. This is in line with the right to self-determination and rights to protection of physical integrity and privacy. In this connection family donor or replacement donor systems have been shown not to meet the criteria of a volunteer system and are therefore undesirable and to be discouraged.

Non-remunerated donation

Blood is regarded in the same light as any other body tissue, so blood donation should be on a non-remunerated basis. There should be no rewarding of the donor with money, merchandise or services.

Protection of the donor

No coercion or pressure should be exerted on potential donors, who should be provided with adequate information about the process to properly consent to donation. Blood should be collected under the overall supervision of a physician. Confidentiality concerning all personal donor details, including laboratory results, should be ensured.

Protection of the recipient

The patient in need of a blood transfusion should, where clinically possible, be provided with reliable information of the risks, benefits and any available alternatives to blood transfusion.

A proper application of the principle of autonomy means that patients needing blood (provided they retain the capacity to understand and assess the information provided) are free to accept or refuse blood transfusion.

Quality assurance is paramount throughout all the stages of blood transfusion starting with the detailed criteria for donor selection or deferral. This also includes the complete range of management and operational systems needed to ensure the safety of blood, blood components or blood products, to prevent adverse reactions and transfusion-transmitted infections.

Self-sufficiency

Blood transfusion does not exist in isolation. It is an integral and indispensable part of a health care system. The public authorities have a responsibility to protect the health of the population and to ensure the availability of services, equity of access to those services and their quality and safety. Inherent in these values is the promotion of national self-sufficiency in blood. Self-sufficiency means that a country provides all the blood it needs from its own resources. If it is not attainable on a national level, then self-sufficiency of a slightly different kind can be achieved through collaboration with other countries in a similar position. Self-sufficiency applies to the source of blood, but not necessarily to the source of essential supplies, equipment, technology and plasma fractionation.

Optimal use of blood and blood products

Taking into account the scarcity of blood and the dangers inherent in its use, transfusion medicine should be properly practised. The risks of blood transfusion mean that blood should not be given to patients who do not need it. Patients who need blood, blood components, or blood products must receive what they need. There are three general types of misuse in transfusion therapy: use of blood products when not clinically justified, use of too little or too much in patients who require transfusion, and use of the wrong component or product in patients requiring transfusion. All these should be avoided.

1.9.6 Molecular biology/genetics

Issues raised by discussions of molecular biology and genetic testing touch upon deeply held convictions about what constitutes a human being or a person, about identity and about the family. Just as these convictions and perceptions vary, so does the way different societies and religions treat these issues. Detailed discussion of these complex areas are beyond the scope of this document.

1.9.7 Research

Biomedical research aimed at understanding and preventing disease or at improving the diagnosis or treatment of disease is highly desirable and is often conducted solely with altruistic motives. Many medical laboratories initiate research themselves and, knowingly or unknowingly, are involved in clinical trials. Unfortunately, there are too many examples where biomedical research has been conducted inappropriately and patients or research subjects have suffered. It is for this reason that medical laboratories should understand the implications of research projects with which they are involved to avoid complicity in unethical research. In many countries a system of institutional ethics committees has added a level of formal oversight to medical research. Even this is not a guarantee that the research is ethical in every respect, and a laboratory should be satisfied that the proposed research meets its own standards. Recommendations and guidelines on biomedical research involving humans are given in Annexes 3 and 4.

The involvement of medical laboratories in biomedical research will usually centre on analysis of tissue or fluids. Some of the issues associated with this are dealt in Section 1.9.9 on human tissues, the major one being that proper consent has been obtained, or proper authority has been given, for the analysis. The following

principles may act as a guide to laboratories initiating their own research or participating in other biomedical research:

- Potential benefits of the research should outweigh the risks.
- The risks of the research should be predictable.
- The patient or research subject should be well informed about proposed treatments, procedures, risks, costs, inconvenience, discomforts and relevant alternatives.
- Consent to participate should preferably not be sought by a doctor in a treating relationship with the patient.
- Due regard should be given to issues of privacy and confidentiality.
- The progress of the research should be regularly reviewed, especially in trials of therapeutic agents.
- In randomized clinical trials, control subjects must receive the best currently available means of prevention, diagnosis or treatment.

Volunteers may be used for non-clinical, non-therapeutic biomedical research, but participation must be free of any coercion or inducement. The pharmaceutical industry has contributed enormously to biomedical research in partnership with the medical profession, research institutions and hospitals. This partnership, however, provides opportunities for questionable practices and flagrant abuses of the ethical principles of biomedical research. Codes of conduct regarding the relationship between doctors and the pharmaceutical industry have been developed. National medical associations should be aware of those most relevant to a particular laboratory. In the absence of this awareness, the following may be of assistance:

- *Ethical guidelines in the relationship between physicians and the pharmaceutical industry*. Sydney, Royal Australian College of Physicians, 1994.
- Physicians and the pharmaceutical industry. Position paper of the American College of Physicians. *Annals of internal medicine*, 1990, 112: 624–6.

1.9.8 HIV/AIDS

Testing for HIV requires special consideration. Tests should normally be performed only on patients who are fully informed of the implications of a positive result. This may require special counselling. Confidentiality is especially important, and it is generally accepted that greater public health gains can be made in preventing the spread of AIDS by ensuring that individuals can be tested and treated with the assurance of confidentiality and sensitivity than by more punitive systems, which often have the effect of driving the whole problem "underground".

In some countries, compulsory testing of certain groups, such as intravenous drug users or prisoners, is required by law. While the wisdom of some programmes may be debated, it is reasonable for a laboratory to participate in the testing even though informed consent may not have been given. In these cases the burden of responsibility for the patient usually rests with the authority organizing the programme, but in some situations, such as testing for visa requirements, where the authorities may have little interest other then the requirement for a negative result, a laboratory could find itself with an obligation to provide counselling and support in the case of an unexpected positive result. The laboratory should ensure that facilities exist for these services to be provided. Screening programmes for epidemiological purposes are acceptable, but if patients with positive results can be identified (and notified) then prior informed consent is required.

Doctors with a dual responsibility both for an affected patient (including specimens from such patients) and for the health and safety of others, such as laboratory staff who may receive needle stick injuries, have a special responsibility. In those situations a doctor may consider that obligations to the new patient (that is, the staff member) supersedes obligations of confidentiality to the first patient. For example, in case of a needle stick injury to a staff member, a doctor may arrange for, say, HIV testing on the "donor" blood (that is, the blood of the first patient) in order that appropriate treatment of the new patient can be determined. Where possible any testing to be carried out on the "donor" blood should be done with the consent of the patient, but there will be situations when this is not possible. Under such circumstances the identity of the patient with the positive test result should be protected as far as possible.

1.9.9 Human tissues and fluids

At any one time, a medical laboratory is the repository of quantities of human tissues and fluids. Such tissues and fluids have many potential uses, including therapeutic purposes, teaching, research or even commercial development. Such tissues and fluids include:

- blood
- urine
- faeces
- biopsy specimens
- surgical or autopsy specimens
- histopathology blocks and slides.

The property status of these tissues and fluids has changed in recent times in some parts of the world. The predominant view is that, the tissue or fluid having been provided, the patient had no continuing right to determine how that tissue or fluid would be used subsequently. The analysis or test having been performed, the tissues or fluid had little more status than abandoned goods and could therefore be dealt with at the discretion of the person in effective control of them (the person in charge of the laboratory). Thus, blood specimens were readily available for research purposes, surgical specimens were "potted" for educational purposes (or even public display), and cell lines even appropriated for commercial purposes[1]. Among the earlier manifestations of changing attitudes was a developing concern with how laboratories dealt with the remains of fetuses, the stillborn, and extremely premature neonates dying within minutes of birth. If the birth was not one that needed to be registered (and sometimes even if it was) the remains were often sent to the hospital incinerator with other laboratory waste or buried, along with other unnamed neonatal deaths, in mass unmarked graves. Mothers (and fathers) began to take exception to this, and were supported by psychologists who pointed out the importance of more formal procedures for dealing with the remains and of helping the parents and other members of the family deal with the bereavement. Such procedures now exist in many laboratories.

The practice of storing and testing blood samples for epidemiological purposes also focused attention on important ethical issues for laboratories. For example, testing batches or large numbers of such samples for HIV antibodies raised issues about contacting patients found to be positive. These patients had not contemplated such a test at the time of providing the blood sample let alone consented to its performance. These and other similar examples have led to formal statements such as that of the Council of Europe:

> When in the course of an intervention any part of the human body is removed, it may be stored and used for a purpose other than that for which it was removed only if this is done in conformity with appropriate information and consent procedures[2].

This means that a surgical specimen, for example, should be "potted" for educational purposes only if the patient has agreed to this use. Properly approached,

---

[1] See *Moore v. Regents of the University of California*, 793 P.2d 479 (Cal. 1990), rev'g 249 Cal. Rptr. 494 (Ct. App. 1988).

[2] Council of Europe. *Convention on human rights and biomedicine. Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine.* Article 22. Adopted by the Committee of Ministers on 19 November 1996.

few patients are likely to have any difficulty with this and most are likely to be pleased that some general benefit can be derived from preserving their specimen.

It also means that femoral heads and other skeletal tissue, for example, which can be processed, banked and later used as allograft material may only be so used if the donor patient has properly given prior consent. This will have the added practical advantage, without which the use of the tissue as allograft is potentially dangerous, of allowing a proper history to be taken and the appropriate extra tests to be performed to minimize the risk of transmitting an infectious disease to the recipient.

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 <u>fully informed</u> 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 <u>exempt</u> 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
<u>Due to HIPAA: Medical record reviews are no longer exempt</u>

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 seratraline (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 seratraline 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 seratraline.

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.

Questons:

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 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

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. Theseare 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.bmjjournals.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 confidentially 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.bmjjournals.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.bmjjournals.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-7/2/448760762fb56502272980730 16d28db

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.globalethics.bham.ac.uk/consultancy/Retained_organs.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 prgram 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 benefitand 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 kittlke 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

<u>Risk</u> 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."

<u>Minimal risk</u> 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.

<u>Benefit</u> 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. <u>Critique this study as though you are an IRB member, assessing the various review elements.</u>

B. <u>Provide constructive suggestions as to how it may be improved to be more acceptable as a human subjects study.</u>

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

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	**Clinical Relevance**
Body-mass index (BMI)	**Obesity**
	Metabolic Syndrome
TSH	**Hyper or hypothyroidism**
Fasting blood sugar	**Glucose intolerance or diabetes**
Depression rating scale	**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** **Coeliad 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 for 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 office 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 facilitatinging osteoblast function without stimulating osteoclasts nearly as much, thus increasing bone density. Phase I and II trials were conducted with no significant morbidity at an effective dose.

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

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

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

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

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

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

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

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

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

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

Case: Asthma Comparison

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

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

The subjects were randomized to 4 groups and treated for 12 weeks: Beclomethasone bid, NUSTER 100 µg bid, NUSTER 200 µg bid, and placebo. Subjects would use albuterol, another standard agent, as needed. The main outcome measure was FEV_1, 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 FEV_1 deteriorated. Ten percent of the active treatment subjects and 44% of the placebo subjects had to discontinue the study because of shortness of breath.

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

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

1. **Was this an ethical study?**

2. **Was a placebo control justified**
    a. **If the subjects were children?**
    b. **If the subjects were adults?**

3. **Seven ethical requirements for clinical research as delineated by Emanuel et al are:**
    a. **scientific value**
    b. **scientific validity**
    c. **fair subject selection**
    d. **favorable risk/benefit ratio**
    e. **independent review**
    f. **informed consent**
    g. **respect for enrolled subjects**

Discuss this study with respect to each of these.

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

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

Case: Alzheimer's Disease

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

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

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

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

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

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

Questions:

1. Would the IRB and the University-Industry Conflict of Interest Committee of your institution have a problem with this study?

2. How will you determine whether participants can consent for themselves? What should you do if some cannot?

3. How will you present the studies to the subjects and to their surrogates?

4. This category of patients experiences a lot of "sundowning." Will this likely affect your study?

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

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

Chapter 3: Bibliography

Experimental Design

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

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

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

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

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

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

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

This is an excellent review of the federal rule that permits research without consent in emergency situations. The detail about the limitations and the arguments about whether personal therapeutic benefit must be part of the process are discussed.
http://www.mssm.edu/msjournal/72/724242.shtml

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

This paper discusses the DSMB stopping rules which, he says, should be built into the design, before efficacy, lack of safety, or inevitably no evidence of benefit. If you belong to a DSMB or have one on your study this is very worthwhile reading.
http://www.nature.com/nrd/journal/v3/n11/abs/nrd1553_fs.html

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

The authors propose to use "component analysis" to assess risk vs. benefit in clinical research. The therapeutic components are assessed differently from the non-therapeutic. They use equipoise to justify the therapeutic component.
http://www.nature.com/nm/journal/v10/n6/abs/nm0604-570.html;jsessionid=00E29673439DE2E30C826750460B6D20

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

Hypothermia may help treat cardiac arrest in children, but it must be applied quickly. A research project studying their potential benefit without prior consent was proposed to the community and substantial support was obtained but the results were far from unanimous. This study requires Federal approval as well. They concluded that making sure that prospective cardiac arrest parents be notified and allowed to decide whether to participate in advance but that timely consent was 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/eaa1fedba809650b94c8231b368ecded

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

This thoughtful article raises a series of ethical dilemmas regarding a study of "consolidation" therapy for women who achieve a complete clinical remission of ovarian carcinoma. They use the actual conduct of the experiment as the basis for discussion and also introduce the special responsibilities of the initial major study to be as complete as possible.
http://theoncologist.alphamedpress.org/cgi/content/full/9/1/3

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

This article summarizes the arguments in this issue of theoretical medicine regarding the challenge of the Children's Health Act of 2001 that provided both funding and the opportunity to loosen restrictions on research with children. it clearly summarizes sophisticated arguments and could introduce the field to a novice.
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/A:1024650410202

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

In research with small children one might ask why are parents consenting. This study queries 44 parents or guardians regarding volunteering their children and found that the leading reason was neither altruism nor free medications, but rather to learn more about the disease. Nicely done.
http://pediatrics.aappublications.org/cgi/content/full/111/5/1037

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

This is an excellent description of the need for research on adolescents, their ability to consent, and the federal rules as interpreted for adolescents.
http://www.sciencedirect.com/science/article/B6T80-49W1YBN-G/2/a66b9af2a5f68c67a6695a167276dbcd

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

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

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

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

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

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

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

Drug trials are very carefully designed. They are approved because they have a favorable risk to benefit ratio. The authors argue that when companies stop trials for commercial reasons rather than matters of safety or efficiency they change the risk to benefit analysis unfavorable and, in doing, violate research ethics. This is an interesting and useful article.
http://jme.bmjjournals.com/cgi/content/full/31/7/410

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

The authors review studies that currently exist regarding the impact of financial incentives to healthy volunteers and discuss the "coercive" impacts of large payments. It sounds a lot like paternalism to me in that the arguments assume that people would violate their interests should they volunteer primarily for money. Who is to say what is in someone's best interests but the person?
http://jcp.sagepub.com/cgi/content/abstract/42/4/365

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

The author analyzes the details of payment for participation in clinical research, mainly in support of appropriate payments.
http://www.jci.org/cgi/content/abstract/115/7/1681

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

This report highlights the productivity of the RADAR (Research on Adverse Drug Events and Reports). The team identified and tried to quantitate 16 adverse reaction to approved drugs that were previously unknown. This study highlights the weaknesses of the adverse event reporting system (or non-system), It lends support toward enhancing the FDA's capacity to utilize the AE reporting system and the huge advantages inherent in developing a national database using electronic medical records.
http://jama.ama-assn.org/cgi/content/full/293/17/2131

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

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

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

This report discusses the evils of contracts with clinical research sponsors in which the investigator doesn't see all of the data before agreeing to publication.
http://content.nejm.org/cgi/content/extract/352/21/2160

Friedrich, M. J. (2005). "Neuroscience Becomes Image Conscious as Brain Scans Raise Ethical Issues." JAMA **294**(7): 781-783.
http://jama.ama-assn.org/cgi/content/full/294/7/781

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

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

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

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

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

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

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

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

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

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

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

Heaney, R. (2003). "Ethical issues in the design of osteoprosis 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 theyown 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 t 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 troglitizone 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 auras 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. Elaborationg 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. <u>Clinical Practice Guidelines</u>

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 he 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' 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 is have to find a way to convince investigators, both clinical and nonclinical, of the serious problems of bias and co-option 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 capitol 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 relationsips. 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 interes, 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 schience, 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 clariton 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 zand 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 reviewed159 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 SADRs 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 wor thwhile 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 discussion the plight of the Fred Hutchison Cancer Research Center when sued by research subjects' families. The issue of the Center or its physicians derving 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.bmjjournals.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 Materal 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 filed 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.bmjjournals.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.bmjjournals.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.

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 "totipotential" 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 totipotential 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 treament 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 pluripotential 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 commodofication 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 involvesomatic 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. The 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: Weighin 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 supportedhe 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

Some call synthetic biology an epochal development—the start of a new industrial revolution, the moment humans learned to be gods. Others think it is an incremental advance with an iffy payoff. In these essays, the chair of the Presidential Commission for the Study of Bioethical Issues and participants from a recent Hastings project examine the social challenge it presents.

The Ethics of Synthetic Biology: *Guiding Principles for Emerging Technologies*

BY AMY GUTMANN

The Presidential Commission for the Study of Bioethical Issues released its first report, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, on December 16, 2010.[1] President Barack Obama had requested this report following the announcement last year that the J. Craig Venter Institute had created the world's first self-replicating bacterial cell with a completely synthetic genome. The Venter group's announcement marked a significant scientific milestone in synthetic biology, an emerging field of research that aims to combine the knowledge and methods of biology, engineering, and related disciplines in the design of chemically synthesized DNA to create organisms with novel or enhanced characteristics or traits. Intense media coverage followed. Within hours, proponents and critics made striking claims about the discovery—ranging from "Frankencell" to the idea of humans "creating life"—often invoking the kind of eye-catching terms that heighten interest, and anxiety, about risks and benefits.

The commission had a unique opportunity to contribute proactively to a field of scientific inquiry that is relatively young. While the synthetic genome is a significant technical achievement, synthetic biology as a field is still in its early stages. Its most promising potential benefits and most worrisome risks are not yet upon us, allowing time for efforts to publicly consider and recommend safe development of this field for the good of all.

The president gave the commission six months to review this emerging science and produce recommendations "to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks."[2] This task fit the commission's mandate to identify and promote "policies and practices that ensure scientific research, healthcare delivery, and technological innovation are conducted in an ethically responsible manner."[3] It also offered the opportunity for the commission to convene in an open and public forum to encourage reasoned deliberation and consideration of public issues, including the impact of new technologies on our collective human well-being and our responsibilities to the environment.

The commission considered the potential risks and benefits of the field, reviewed the technology in the context of essential conceptions of human agency and life, as well as the human relationship to nature, and unanimously concluded that the field of synthetic biology does not require new regulation, oversight bodies, or a moratorium on advancing research *at this time*. But these concerns, along with uncertainties about how the field may develop in the future, were central to the commission's unanimous conclusion that responsible stewardship requires that existing federal agencies conduct an ongoing and coordinated review of the field's risks, benefits, and moral objections as it matures.

The commission calls this strategy "prudent vigilance." Some commentators mistook these conclusions as a pass on any restraint of this emerging science.[4] Rather, the commission called not only for more coordinated agency oversight and monitoring of risks and benefits, but also for experts and policy-makers to actively and openly engage in public dialogue as the science evolves, so that all concerned citizens can understand and offer their own perspectives on what lies ahead. The commission worked to model such public outreach in its

Amy Gutmann, "The Ethics of Synthetic Biology: Guiding Principles for Emerging Technologies," *Hastings Center Report* 41, no. 4 (2011): 17-22.

deliberations, and in its conclusions underlined the responsibility of experts, policy-makers, and federal agencies to carry forward this critical work of public feedback, education, and outreach.

The Commission's Deliberations

The commission held meetings in Washington, D.C., Philadelphia, and Atlanta that provided opportunities for its members to deliberate publicly and to hear from nearly three dozen invited experts on scientific, ethical, and policy aspects of synthetic biology and its applications. At each meeting, time was set aside for public comments, and the commission heard a range of perspectives on the future of synthetic biology. Several dozen additional public comments were received in writing following published requests for comment from the commission.

The guests who spoke at our meetings and the public comments that we received highlighted the remarkable potential benefits that synthetic biology may yield for human health, energy, agriculture, and other areas. They also discussed the range of risks associated with research and commercial development of these advances and the significant uncertainty regarding both the likelihood and magnitude of those risks and benefits.

Most previous and ongoing analysis of synthetic biology has examined specific policy and ethical issues, focusing, for example, on the evaluation of risks and benefits and strategies to optimize that balance.[5] Some other work has looked at the field more broadly and begun analyzing the fundamental concerns that it may raise by considering the work in the context of essential conceptions of human agency and life; its overall impact on biodiversity, ecosystems, or food and energy supplies; and its impact on the balance between humans and nature.[6] Some of this research extends beyond issues unique to synthetic biology to concerns common among emerging technologies or for biotechnology overall.

Since much of this broader analysis is still in its infancy, President Obama's request gave the commission an exceptional opportunity to look forward instead of to merely react, and to lead a proactive review of this emerging field. The commission aimed to learn from the collective insights of the ongoing research in the science and ethics of synthetic biology and to consider how best to translate these at times conflicting perspectives into actionable recommendations for the federal government. In light of the parallels between the ethical issues raised by synthetic biology and those of emerging technologies generally, the commission developed a set of basic principles that may be applicable to the ethical analysis of all emerging technologies, including those already present and others that develop in the future.

Principles for Assessing Emerging Technologies

The commission found many efforts to shape policy, governance, and regulation related to synthetic biology, but few examples of a broad-based ethical framework upon which to base such proposals. We identified five ethical principles relevant to the social implications of synthetic biology and other emerging technologies and used these to guide our evaluation of the current state of synthetic biology and its potential risks and benefits, as well as our policy recommendations.

The guiding principles are: (1) public beneficence, (2) responsible stewardship, (3) intellectual freedom and responsibility, (4) democratic deliberation, and (5) justice and fairness. These principles are intended to serve as provisional guideposts subject to refinement, revision, and comment.

Public beneficence. The ideal of public beneficence is to act to maximize public benefits and minimize public harm. This principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. In the case of emerging technologies, this improvement may be by means of providing improved or more widely available forms of medical and health care, food, shelter, transportation, clothing, and eco-friendly fuel, along with other means of improving people's lives. Scientific and technological discoveries often have the added potential of increasing economic opportunities, which also redound to the public good.

The principle of beneficence should be applied beyond the individual level—the focus of beneficence in the *Belmont Report*—to the institutional, community, and public levels, while not overlooking possible harms and benefits to individuals.[7] Policy-makers should adopt a societal perspective when deciding whether to pursue particular benefits of emerging technologies in the face of risks and uncertainty. If considering whether to restrict these pursuits, a similar examination of community interests and potential positive and negative impacts is essential. When seeking the benefits of synthetic biology and other emerging technologies, public beneficence requires the public and its representatives to be vigilant about harms and prepared to revise policies that pursue potential benefits with insufficient attention to risks.

Responsible stewardship. Among living beings, humans are in a unique position to be responsible stewards of nature, the earth's bounty, and the world's safety. Responsible stewardship recognizes the need for citizens and their representatives to think and act collectively for the betterment of all, especially those who cannot represent themselves. Benefits and risks extend to current and future human generations, nonhuman species, and the environment, each with unique needs and vulnerabilities. Emerging technologies present particularly profound challenges for responsible stewardship because our understanding of the potential benefits and risks is incomplete, preliminary, and uncertain. The possibility of intentional misuse by malicious actors further complicates efforts to respond adequately to benefits and risks.

Responsible stewardship addresses these varied challenges by calling for actions that embrace potential benefits while simultaneously mitigating risks over time and across populations. It calls for broader risk-benefit discussions than

would typically be required based on a concern for public beneficence alone. The principle of responsible stewardship rejects two extreme approaches: an extreme action-oriented approach that pursues technological progress without limits or due regard for public or environmental safety, and an extreme precautionary approach that blocks technological progress until all possible risks are known and neutralized. While the action-oriented approach is irresponsibly brazen, the precautionary approach is overly wary. Both fail to carefully assess the most likely and significant benefits against the most likely and significant harms. Through the development of agile, measured oversight mechanisms, responsible stewardship rejects positions that forsake potential benefits in deference to absolute caution and positions that ignore reasonably foreseeable risks to allow unfettered scientific exploration.

This principle is applied to emerging technologies through open decision-making processes informed by the best available science. Responsible stewardship calls for "prudent vigilance": establishing processes for assessing likely benefits along with safety and security risks both before and after projects are undertaken. A responsible process will continue to evaluate safety and security as technologies develop and diffuse into public and private sectors, and will also include mechanisms for limiting their use when indicated.

When seeking the benefits of synthetic biology, we must be vigilant about harms and prepared to revise policies that pursue potential benefits with insufficient attention to risks.

Prudent vigilance does not demand extreme aversion to all risks. Not all safety and security questions can be definitively answered before projects begin, but prudent vigilance does call for ongoing evaluation of risks along with benefits. The iterative nature of this review is a key feature of responsible stewardship. It recognizes that future developments demand that decisions be revisited and amended as warranted by additional information about risks and potential benefits.

Intellectual freedom and responsibility. Democracies depend on intellectual freedom, coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Sustained and dedicated creative intellectual exploration is critical for expanding the boundaries of human knowledge and achievement, developing innovative technologies that can compete in the global marketplace, and fostering collaborations among industry, academe, and government that yield useful products, tools, and policies. While some potentially beneficial emerging technologies could also be put to malevolent "dual use," these risks alone are generally insufficient to justify limits on intellectual freedom. Public policy must promote the creative spirit of scientists and unambiguously protect their intellectual freedom because creative and complex intellectual explorations, sustained over time, promote scientific and technological progress.

At the same time, the history of science is sadly full of examples of intellectual freedom exercised without responsibility, resulting in appalling affronts to vulnerable populations, the environment, and the ideals of science itself. Scientists who act irresponsibly are capable of harming not only themselves and other individuals, but also their communities, their nations, and international relations.

As a corollary to the principle of intellectual freedom and responsibility, the commission endorsed a principle of *regulatory parsimony*, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good. Regulatory parsimony is especially important in emerging technologies—still in formation by their very definition—where the temptation to stifle innovation on the basis of uncertainty and fear of the unknown is particularly great. The blunt instruments of statutory and regulatory restraint may not only inhibit the distribution of new benefits, but can be counterproductive to security and safety by preventing researchers from developing effective safeguards. With sufficient freedom to operate, tomorrow's achievements may render moot the risks of today.

Democratic deliberation. The principle of democratic deliberation reflects an approach to collaborative decision-making that embraces respectful debate of opposing views and active participation by citizens. It calls for individuals and their representatives to work toward agreement whenever possible and to maintain mutual respect when it is not. At the core of democratic deliberation is an ongoing, public exchange of ideas, particularly regarding the many topics—in science and elsewhere—in which competing views are advocated, often passionately. A process of active deliberation and justification promotes an atmosphere for debate and decision-making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests.

Importantly, democratic deliberation recognizes that while decisions must eventually be reached, those decisions need not (and often should not) be permanently binding,

particularly when subsequent developments warrant additional examination. An ongoing and dynamic deliberative process recognizes the importance of challenging previously reached conclusions in light of new information and is by its very nature able to correct the inevitable mistakes that arise in collective decision-making.

The principle of democratic deliberation is particularly well suited to the assessment of emerging technologies. These fields offer the promise of remarkable potential benefits to science and society, yet they also raise risks regarding unintended consequences or possible malicious use. Each of these areas is clouded by uncertainty and incomplete information, complicating efforts to promote innovation while minimizing the likelihood of harm. Finding this balance demands careful ongoing review of the science and its applications. It presents an ideal opportunity for broad engagement and dialogue among the scientific community, policy-makers, and the citizenry, both by fostering conversation and debate among scientific and policy experts and by spurring meaningful outreach and education for the lay public.

Justice and fairness. The principle of justice and fairness relates to the distribution of benefits and burdens across society. Emerging technologies like synthetic biology affect all persons, for good or ill. Society as a whole has a claim toward reasonable efforts on the part of both individuals and institutions to avoid unjust distributions of the benefits, burdens, and risks that such technologies bring. This same claim extends internationally to all those who may be affected—positively or negatively—by synthetic biology and its applications. A fundamental principle of fairness suggests that society should seek to ensure that the benefits and burdens of new technologies are shared as much as possible.

A commitment to justice and fairness is a commitment to ensuring that individuals and groups share in the benefits of new technologies and that the unavoidable burdens of technological advances do not fall disproportionately on any particular individual or group. Technological innovation benefits from public investment and from societal contribution toward safe and supportive research environments, and so it is reasonable that society expects a return on that investment.

Justice and fairness extend not only from individual societies to their constituents but also from individual societies to the international community overall. Emerging technologies can and likely will have global impacts. For that reason, every nation has a responsibility to champion fair and just systems to promote the widest availability of information, the broadest distribution of beneficial technologies, and the most expansive culture of responsibility for biosafety and biosecurity.

Applying These Principles to Synthetic Biology

The commission's development of an ethical framework concurrently with its specific policy recommendations differs from the approach of earlier bioethics advisory bodies, which formulated principles and conclusions only after several years of study and debate. By taking this approach, the commission encouraged constructive public debate by making explicit the values underlying particular policy recommendations.

The extraordinary promise of synthetic biology to create new products for clean energy, pollution control, and medicine; to revolutionize chemical production and manufacturing; and to create new economic opportunities comes with a concurrent duty to attend carefully to potential risks, be responsible stewards, and consider thoughtfully the implications for humans, other species, nature, and the environment. While future developments may raise further objections, the commission unanimously recommended that no additional federal regulations or a moratorium on work in this field be enacted at this time. Instead, the commission urged ongoing government monitoring and dialogue between the private and public sectors.

The commission's eighteen recommendations are organized according to the five ethical principles outlined earlier. While many of the recommendations are directed to the federal government, our report also highlights the role of citizens and experts, including the absolutely critical role of the scientific community in promoting an environment that allows emerging biotechnologies to flourish yet remains sensitive to known and anticipated risks.

Among the recommendations arising from the principle of public beneficence are a coordinated review of public funding for synthetic biology research (including research on ethical and social issues) and an examination to ensure that research licensing and sharing policies are sufficient to promote innovation.

Working from the principle of responsible stewardship, the commission endorsed neither a moratorium on synthetic biology until all risks are identified and mitigated, nor unfettered freedom for scientific exploration. Instead, the commission embraced a middle ground—an ongoing process of prudent vigilance that carefully monitors, identifies, and mitigates potential and realized harms over time. To promote clarity, coordination, and accountability across the government, the commission recommended that the Executive Office of the President lead an interagency process to evaluate existing oversight authorities and ensure that the government remains informed of developments, risks, and opportunities as this field grows. In light of the interdisciplinary character of synthetic biology, ethics education similar or superior to the training required today in the medical and clinical research communities should be developed and required for all researchers and student-investigators outside the medical setting, including in engineering and materials science.

The commission recommended revisiting the moral objections to synthetic biology as the field advances, but we were not persuaded that synthetic biology currently fails to respect the proper relationship between humans and nature. The commission believes that opposition to synthetic

biology on such grounds alone does not adequately reflect the relationship of the technology to previous scientific activities and the current limited capabilities of the field.

The question relevant to the commission's review of synthetic biology was whether this field brings unique concerns that are so novel or serious that special restrictions are warranted at this time. Based on our deliberations, the commission concluded that special restrictions are not needed, but that prudent vigilance can and should be exercised. As our ability to engineer higher-order genomes using synthetic biology grows, other deliberative bodies ought to revisit this conclusion.

Recommendations based on the principle of intellectual freedom and responsibility direct the government to support a continued culture of responsibility among individual researchers and research institutions, coupled with institutional monitoring, enhanced watchfulness, and the expanded application of relevant regulations, if necessary. Also recommended are periodic assessments of safety and security risks and the applicability of current oversight practices.

The importance of ongoing dialogue is central to the commission's recommendations related to democratic deliberation. These recommendations endorse continued exchanges among scientific, religious, and civil society groups as synthetic biology develops, and they call on all individuals and groups to describe the capabilities and limitations of the field accurately and clearly. To further promote public education and discourse, we support the creation of a privately managed online tool to check the veracity of public claims regarding advances in synthetic biology. These activities would be enhanced by comprehensive programs to improve scientific and ethical literacy among all age groups, regarding both synthetic biology and science generally.

From the principle of justice and fairness, the commission recommends an evaluation of current requirements and alternative models to ensure that the risks of research in synthetic biology—including for human subjects and other affected parties—are not unfairly or unnecessarily distributed. A companion recommendation encourages manufacturers and others seeking commercial applications for synthetic biology to manage risks and potential benefits to communities and the environment so that the most serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These groups should strive to make available the important advances that may result from this research to those individuals and populations who could most benefit from them.

A responsible process will continue to evaluate safety and security as technologies develop. It will also include mechanisms for limiting their use when indicated.

Bioethics Commissions and Public Dialogue

Only with an ongoing, open, and well-informed discourse can our society realistically hope to reap the benefits of scientific progress with due regard for the serious concerns that new biotechnologies always raise. Without an open and well-informed dialogue, we risk grave harm, not least to the public support upon which the scientific enterprise is built.

While by no means a substitute for robust, ongoing exchanges among citizens, the scientific community, and policy-makers, the commission's deliberations on this matter sought to provide an inclusive forum for discussion. Our hope is that the commission's recommendations will be a catalyst for future deliberations among other groups interested in synthetic biology.

To that end, the commission was pleased by the interest in and reactions to our report following its release in December 2010. Stakeholder individuals and groups—including university-based scientists, biotechnology firms, bioethicists, religious organizations, and others—responded largely favorably to the commission's assessment and recommendations. Early reactions to the principle of prudent vigilance as an appropriate approach to the ongoing assessment of the risks and benefits of synthetic biology were similarly positive overall, coming from individuals and groups representing a range of perspectives regarding biotechnology and its regulation.

A coalition of civil society organizations was more skeptical of the merits of prudent vigilance. In comments to the media and in an open letter to the commission and government officials, these groups argued that the precautionary principle ought to guide the regulation of synthetic biology.[8] Based on certain conceptions of the precautionary principle, these groups advocate "a moratorium on the release and commercial use of synthetic organisms until a thorough study of all the environmental and socio-economic impacts of this emerging technology has taken place."

Throughout its work, the commission was particularly sensitive to ensuring that the government remains attentive to the risks related to synthetic biology, including risks that may emerge as the field matures. It concluded that an

approach characterized by prudent vigilance allows policymakers to continue assessing safety and security as technologies develop, and to include mechanisms for limiting their practical applications and use when necessary. Prudent vigilance shares with the precautionary principle a concern for identifying and mitigating risks. However, it advocates continued progress in the pursuit of potential benefits in tandem with that ongoing sensitivity to risks and the development of appropriate responses. The commission believes that prudent vigilance will prove to be a valuable approach to the assessment of risks related to synthetic biology and other emerging technologies. We welcome ongoing debate and discourse in light of existing literature on the precautionary principle and conventional risk analysis practices.

1. Presidential Commission for the Study of Bioethical Issues, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* (Washington, D.C.: Government Printing Office, 2010), from which parts of this article are based.

2. Letter from President Barack Obama to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, May 20, 2010, http://bioethics.gov/documents/Letter-from-President-Obama-05.20.10.pdf.

3. Executive Order no. 13521, "Establishing the Presidential Commission for the Study of Bioethical Issues," *Federal Register* 74, no. 228 (November 30, 2009), http://www.bioethics.gov/documents/Executive-Order-Establishing-the-Bioethics-Commission-11.24.09.pdf.

4. A. Pollack, "US Bioethics Commission Gives Green Light to Synthetic Biology," *New York Times*, December 16, 2010; J. Kaiser, "Synthetic Biology Doesn't Require New Rules, Bioethics Panel Says," *Science Insider*, December 16, 2010, http://news.sciencemag.org/scienceinsider/2010/12/synthetic-biology-doesnt-require.html?ref=hp; J. Walsh, "Presidential Commission Gives Synthetic Biology the Green Light," *Discover*, December 16, 2010, http://blogs.discovermagazine.com/80beats/2010/12/16/presidential-commission-gives-synthetic-biology-the-green-light/; letter to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, December 16, 2010, http://www.foe.org/sites/default/files/Letter_to_Commission_Synthetic_Biology.pdf.

5. National Science Advisory Board for Biosecurity (NSABB), *Addressing Biosecurity Concerns Related to Synthetic Biology*, April 2010 draft report (Washington, D.C.: National Institutes of Health, 2010), http://oba.od.nih.gov/biosecurity/pdf/NSABB%20SynBio%20DRAFT%20Report-FINAL%20(2)_6-7-10.pdf; E. Parens, J. Johnston, and J. Moses, "Ethical Issues in Synthetic Biology: An Overview of the Debates," Woodrow Wilson International Center for Scholars, June 24, 2010, http://www.synbioproject.org/library/publications/archive/synbio3/; S. Miller and M.J. Selgelid, *Ethical and Philosophical Consideration of the Dual-Use Dilemma in the Biological Sciences* (Dordrecht, the Netherlands: Springer, 2008); European Commission, *Synthetic Biology: Applying Engineering to Biology – Report of a NEST High-Level Expert Group,* (Luxembourg: Office for Official Publications of the European Communities, 2005), ftp://ftp.cordis.europa.eu/pub/nest/docs/syntheticbiology_b5_eur21796_en.pdf; Organization for Economic Co-Operation and Development and the Royal Society, *Symposium on Opportunities and Challenges in the Emerging Field of Synthetic Biology: Synthesis Report* (Paris, France: OECD and Royal Society, 2010), http://www.oecd.org/sti/biotechnology/synbio.

6. A.A. Snow et al., "Genetically Engineered Organisms and the Environment: Current Status and Recommendations" *Ecological Applications* 15, no. 2 (2005): 377-404, http://www.biosci.ohio-state.edu/~asnowlab/Snowetal05.pdf; ETC Group (Action Group on Erosion, Technology, and Concentration), *Extreme Genetic Engineering: An Introduction to Synthetic Biology* (Ottawa, Ontario, Canada: ETC Group, 2007), http://www.etcgroup.org/upload/publication/602/01/synbioreportweb.pdf; B.G. Norton, *Sustainability: A Philosophy of Adaptive Ecosystem Management* (Chicago, Ill.: University of Chicago Press, 2005).

7. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: U.S. Government Printing Press, 1979).

8. Letter to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, December 16, 2010, http://www.foe.org/sites/default/files/Letter_to_Commission_Synthetic_Biology.pdf.

Staying Sober about Science

BY ROB CARLSON

Biology, we are frequently told, is the science of the twenty-first century. Authority informs us that moving genes from one organism to another will provide new drugs, extend both the quantity and quality of life, and feed and fuel the world while reducing water consumption and greenhouse gas emissions. Authority also informs that novel genes will escape from genetically modified crops, thereby leading to herbicide-resistant weeds; that genetically modified crops are an evil privatization of the gene pool that will with certainty lead to the economic ruin of small farmers around the world; and that economic growth derived from biological technologies will cause more harm than good. In other words, we are told that biological technologies will provide benefits and will come with costs—with tales of both costs and benefits occasionally inflated—like every other technology humans have developed and deployed over all of recorded history.

Rob Carlson, "Staying Sober about Science," *Hastings Center Report* 41, no. 4 (2011): 22-25.

The Queensland Biotechnology Code of Ethics is currently being updated. This is an interim version.

If you have any queries, please use the contact details on the Queensland Biotechnology Code of Ethics page of the Queensland Science website

Queensland Biotechnology Code of Ethics

Update of the Code of Ethical Practice for Biotechnology in Queensland

General principles of the Code

As a biotechnology organisation, we will observe the following principles:

- **Integrity** – maintaining honesty and respect for the truth.
- **Beneficence and non-maleficence** – achieving the greatest possible good while doing the least possible harm.
- **Respect for persons** – treating patients, clients, research subjects and consumers as autonomous agents having freedom of choice, dignity and human rights.
- **Respect for the law and system of government** – complying with relevant laws and standards, fostering public participation and transparency in decision making, and demonstrating accountability for actions and use of resources.
- **Justice** – recognising wider community interests beyond the interests of the individual, organisation or corporation, providing redress for the vulnerable, and promoting equitable access to resources.
- **Care and protection of animals** – ensuring that the welfare of animals used for scientific purposes is respected.

Having regard to these fundamental principles, and the conduct outlined in this Code, we will pursue biotechnology activities with potential to improve human health, enhance quality of life, support the environment (by observing the precautionary principle, preserving ecosystem health and biodiversity), and promote sustainable agriculture and industry.

The Code

By subscribing to the Code, organisations agree to the following undertaking:

Integrity of research and product testing, risk assessment and risk management

1. We will ensure that staff are made aware of the Code and all other laws, standards and guidelines relevant to the safe and ethical conduct of biotechnology activities conducted by their organisations.

2. We will ensure that research and product testing are performed by qualified persons to optimal scientific standards and are conducted with integrity and with full regard to relevant facts and data.

3. We will maintain accurate and comprehensive records of research and product testing, (both positive and negative) and will report fully and accurately on the results of research, product trials and clinical trials as required by the appropriate regulatory authorities and professional standards.

4. In the conduct of research, product trialling, manufacturing or other biotechnology activities, potential conflicts of interest may arise. Whilst not necessarily unethical, conflicts of interest may result in poor decisions or, at worst, misleading or corrupt behaviour. We will manage and disclose such conflicts of interest to ensure that the integrity of research, product trials, manufacturing or other biotechnology activities, conducted by our organisation is maintained.

5. We will establish systems to ensure that conflicts or potential conflicts of interest are disclosed and that reasonable steps are taken to address and resolve any conflict. There steps are outlined in Appendix I of this Code.

6. We will work with relevant state and federal authorities (for example statutory regulators) and relevant advisory bodies (for example Human Research Ethics Committees and Institutional Biosafety Committees) to ensure that biotechnology products and other biotechnology activities are fully assessed for adverse impacts on human or animal safety or the environment. To the fullest extent possible, we will address long-term as well as short-term impacts, including consequences that may not be immediately apparent. Risk assessments will be conducted in accordance with accepted scientific principles. Where risks are identified, we will ensure that these risks are acknowledged through an open and accountable process and that they are managed in an appropriate manner to minimise the impacts of these risks.[5]

7. We will not proceed with product development where assessed risks outweigh benefits, or where product development or commercial release is not approved by relevant regulatory authorities.

8. We will promptly report any risk or adverse consequence associated with research, or product development, to the relevant authority responsible for product oversight, regulation, risk assessment or risk management. If, following product approval, we become aware of risks or adverse consequences associated with the product that were not known or fully apparent at the time of approval, we will promptly inform the relevant authority.

Research into genetically modified organisms (GMOs)

The Queensland Government developed the *Gene Technology Act 2001* (Qld) as part of the nationally consistent approach to regulating GMOs. The scheme was established by the Commonwealth and all state and territory Governments and is based on a science-based risk assessment process overseen by the independent Gene Technology Regulator. The purpose of this scheme is to ensure that gene technology research and its products are regulated and managed to minimise impacts on human safety and the environment.

9. We will ensure that research into GMOs meets all the requirements of the scheme, noting that failure to comply with the scheme may attract severe penalties. In particular:

   - We will not conduct research into GMOs unless our organisation is accredited by the Gene Technology Regulator. As part of the accreditation process, we will establish Institutional Biosafety Committees (IBCs) to oversee and monitor research within the organisation and to help ensure that the requirements of the national scheme are observed[6].

[5] The Australian New Zealand Standard on Risk Management AS/NZS 4360:2004 may provide a useful tool which includes sound risk management principles.
[6] Smaller institutions may use another organisation's Institutional Biosafety Committee if this is approved by the OGTR.

- We will not conduct contained research on GMOs unless our laboratories are certified by the Gene Technology Regulator to the appropriate containment level.
- We will not undertake contained research, field trials, or commercial releases of GMOs unless these activities have been reviewed and, where appropriate, licensed.
- Where contained research, field trials or commercial releases are approved, we will comply with any conditions established by the Gene Technology Regulator, report any breaches of these conditions and will undertake any corrective action necessary or as directed.
- We will cooperate with Commonwealth officers appointed by the Gene Technology Regulator to monitor compliance with the national scheme.

Biodiscovery

Article 15 of the United Nations *Convention on Biological Diversity* (1993) (the Convention) recognises the sovereign rights of states over their natural resources and their authority to determine access to genetic resources. The Commonwealth has ratified the Convention, the objects of which are the:

- conservation of biological diversity
- sustainable use of the components of biodiversity
- fair and equitable sharing of benefits arising from the use of genetic resources.

10. In this regard, the State Government developed the *Biodiscovery Act 2004*. The *Biodiscovery Act 2004* (Qld) creates a streamlined, environmentally responsible access regime to permit collection of native biological material and requires sharing of benefits derived from the state's biodiversity.

- We will comply with the *Biodiscovery Act 2004* (Qld).
- We will collect native biological material from state land and Queensland waters only with the prior informed consent of the state.
- Before collecting samples from privately owned land, we will ensure that the prior informed consent of the landowner is obtained and we will negotiate reasonable benefit sharing arrangements with the landowner in return for access to the samples.
- We recognise that there may be culturally significant aspects of the knowledge of Aboriginal and Torres Strait Islander people, that we will treat in a sensitive and respectful manner if used in the course of biotechnology.
- Where in the course of biodiscovery we obtain and use traditional knowledge from indigenous persons, we will negotiate reasonable benefit sharing arrangements with these persons or communities.
- In the course of biodiscovery activities we will comply with the *Native Title Act 1993* (Cth).
- We will not commit acts of biopiracy and will not assist a third party to commit such acts.[7]

Care and protection of staff and the public

11. We will comply with all relevant requirements of the *Workplace Health and Safety Act 1995* (Qld) and will seek to comply with relevant Australian Standards governing laboratory safety.

12. We will institute adequate safety measures, and conduct our work in such a way as to ensure the health and safety of our staff and other persons, and we will ensure that our staff are properly trained in safety procedures.

Care and protection of animals

13. To ensure that the welfare of animals used for scientific purposes is respected, we will comply with the *Animal Care and Protection Act 2001* (Qld) and the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.[8]

Transport of materials

14. When transporting biological materials or substances classified as dangerous, we will comply with all relevant international, Commonwealth and State guidelines governing safety in transport.[9]

Supporting discussion of ethical issues and resourcing ethics committees

15. We will encourage consideration and discussion of ethical issues.

16. We uphold the right of all persons to contribute to the debate and discussion about the ethical challenges created by biotechnology. We agree that many ethical issues cannot be resolved purely by the organisation or relevant profession engaged in the research, and that broader perspectives need to be engaged. We will seek to include these broader perspectives in our consideration of ethical challenges.

[7] Biopiracy" refers to the appropriation of developments or discoveries involving biological resources by another party without consent.
[8] The *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* has been endorsed by the NHMRC, CSIRO, Australian Research Council and the Australian Vice Chancellors' Committee. The Code aims to ensure that the welfare of animals used in research is considered, the use of animals is justified, pain or distress to animals is avoided, and the number of animals used in projects is minimised.
[9] For example, the *Transport Operations (Road Use Management - Dangerous Goods) Regulation 1998* (Qld) and *The Australian Dangerous Goods Code*, 6th Edition.

17. We will ensure that all ethics and biosafety committees established within our organisation under relevant laws and guidelines, or under the Code, are given the support necessary to fulfil their responsibilities. This includes ensuring that they have adequate resources, have sufficient standing in the organisation, and have full and appropriate access to senior management. These committees include Human Research Ethics Committees, Animal Ethics Committees, Institutional Biosafety Committees and any committee or body established by the organisation for the purpose of promoting internal discussion of ethical issues or overseeing implementation of the Code.

Intellectual property and commercialisation

18. We will endeavour to ensure that new discoveries by Queensland researchers are developed in ways that provide appropriate returns to the state and, where appropriate, retain control of the intellectual property within Queensland. Where, despite best endeavours, it is not possible to develop our discoveries within Queensland, we will aim to license rather than sell the intellectual property.[10]

19. Recognising that many non-western and developing countries are also seeking to improve their biotechnology capacity, we will support exchange of technology between countries, including developing countries, for the broader benefit of the world economy and social development.

Consumer and patient information

20. We will provide clear, honest and verifiable information to consumers, patients and recipients about our products, the technologies employed, the materials used, and any risks or side effects.

Biological weapons

21. Noting that Australia is a signatory to the *Geneva Protocol* (1925) and the *Biological Weapons Convention* (1972), we will not use biotechnology to develop or produce biological weapons for use in warfare or terrorism, and will not assist any other organisation, person or country to develop, produce, duplicate, stockpile, acquire, retain or use such weapons in Australia or elsewhere.

22. We will aim to ensure that biological control agents directed at environmental protection and agriculture (for example in relation to the control of pests) are ecologically sustainable. We will ensure that such applications comply with relevant laws and biosafety requirements.

Import and quarantine controls

23. We will comply with all national standards administered by the Australian Quarantine and Inspection Service, Biosecurity Australia and the Australian Customs Service when importing or exporting biotechnology products or materials.

International obligations

24. We will observe all relevant laws and standards applicable to other countries in which we conduct biotechnology activities or to which we export biotechnology research or products.[11]

Agriculture, food and the environment

25. Where we deal with agricultural, food and environmental biotechnology, we will aim to produce animal diagnostics and vaccines, crop varieties and biotechnology solutions that benefit consumers, improve agricultural productivity and sustain the environment.

Biodiversity and sustainable agriculture

26. Having regard to the uniqueness of the Australian environment, we will seek commercial release in Australia of genetically modified plants, animals or other organisms only where they have undergone adequate field trialling under Australian conditions in accordance with requirements set down by the Gene Technology Regulator.

27. We will seek to ensure that plants, animals and other organisms produced through gene technology do not interact with natural ecosystems in ways that may diminish Australia's natural ecological capital.

[10] For more information, refer to Chapter 3.3 Ownership of Intellectual Property, Queensland Public Sector Intellectual Property Guidelines.
[11] For example the United Nations Educational, Scientific and Cultural Organisation's (UNESCO) Universal Declaration on Bioethics and Human Rights (http://www.pre.ethics.gc.ca/english/pdf/links/Unescodeclaration_2005.pdf).

28. A key community concern is the risk of unintended mixing on farms and along the supply chain of the harvested products from genetically modified (GM) crops and traditional crops. In addition to the quality assurance protocols, market pressures, and common law provisions that facilitate the adoption of coexistence measures, the Government has developed *A framework to develop co-existence strategies for GM and non-GM crops in Queensland* to ensure effective segregation[12] along the supply-chain and to provide agricultural products that meet market requirements. We will work with the Queensland Government to support the Coexistence Framework.

29. If prescribed by the Gene Technology Regulator, we will establish and maintain adequate buffer zones around genetically modified crops to minimise unwanted transfer to conventional crop varieties, other organisms, or the environment, and will comply with all relevant conditions established by the Gene Technology Regulator.

30. Where we use gene technology applications in animals we will refer to the Gene Technology Regulator, the *Animal Care and Protection Act 2001* (Qld), the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, and requirements of the local Animal Ethics Committee and Institutional Biosafety Committee.

31. Recognising that some traditional technologies have had significant environmental and ecological impacts that have only become apparent over time, we will cooperate with national and state authorities in monitoring the long term ecological impact of modern agricultural biotechnologies.

Consumers

32. Where we deal with food products developed using gene technology we will ensure that the food products meet the highest standards of safety, nutrition and benefit for consumers, and comply with relevant standards developed by Food Standards Australia New Zealand (FSANZ) and approved by the Australia New Zealand Food Regulation Ministerial Council.

33. To ensure consumers have freedom of choice, we will comply with the strict mandatory labelling requirements outlined in the Australia New Zealand Food Standards Code (FSANZ Standard 1.5.2) which requires genetically modified food and ingredients to be labelled as such.

Agricultural and veterinary chemicals

34. We will ensure that agricultural or veterinary chemicals produced through biotechnology are submitted to the Australian Pesticides and Veterinary Medicines Authority for pre-market safety assessment and registration.

Bioremediation and bioprocessing

35. We support the development of biotechnology solutions that deliver cleaner industrial and municipal processes to protect the environment and promote sustainable industries.

36. While acknowledging the potential for bioprocessing technologies to promote ecological and industrial sustainability (by eliminating harmful waste and generating alternative energy sources) we will seek to ensure that these technologies do not themselves threaten the environment or human health or safety. For example, we will ensure that fermentation, biogas production, and other biological processes employed do not pose unacceptable health risks to staff or other persons, and that development of new or enhanced bioprocessing industries utilising agricultural products are assessed for their impact on agricultural systems, ecosystems, land clearing, and water resources.

Medical research and health care

37. We will conduct any research involving humans with the highest standards of safety, integrity and respect for human dignity and will comply with all relevant National Health and Medical Research Council (NHMRC) guidelines as enforced from time to time, in particular the *National Statement on Ethical Conduct in Research Involving Humans* (1999). [13]

38. To ensure biotechnology-based medicines and procedures meet the highest standards of safety and efficacy, we will comply with the *Therapeutics Goods Act 1989* (Cth) and any requirements of the Therapeutics Goods Administration.

39. We will ensure that research involving humans is conducted only with the free, informed and voluntary consent of individuals participating in the research.[14]

40. We will not allow unauthorised access, use, modification or disclosure of personal identifying information gained or used in the course of research without the consent of the individuals identified by that information.[15]

[12] Effective segregation is defined in the Queensland Government publication *Developing strategies for GM and non-GM crops in Queensland – A framework for co-existence* as the "ability to grow and manage along the supply chain both GM and non GM crops in a way that avoids unwanted mixing and delivers products below predetermined market thresholds".

[13] The *National Statement on Ethical Conduct in Research Involving Humans (1999) is currently under review* (http://www7.health.gov.au/nhmrc/publications/humans/contents.htm).

[14] In the event that consent is not readily obtainable, we will look to the *Guardianship and Administration Act 2000* (Qld), the *Powers of Attorney Act 1998* (Qld), the *National Statement on Ethical Conduct in Research Involving Humans*.

[15] Disclosure of personal information is subject to guidelines outlined in the *National Statement on Ethical Conduct in Research Involving Humans*. Disclosure of patient data held by Queensland Government health authorities is governed by legal protections prescribed in the *Health Services Act 1991* (Qld).

Genetic testing

We acknowledge the principle in the *Universal Declaration on the Human Genome and Human Rights (1997)* that "everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics and that dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity".[16]

41. We will not conduct tests for genetic conditions, or potential disease traits in individuals or their offspring, without the free, informed, and voluntary consent of the individuals to be tested.

42. We will not disclose personal, identifying data from genetic tests to third parties without consent of the individuals concerned – restrictions on disclosure are necessary to maintain patient confidentiality and ensure that the results of genetic testing are not used to stigmatise individuals or cause discrimination (for example, with respect to accessing life insurance or employment).

43. We will provide appropriate counselling and support to individuals prior to and after genetic testing to assist individuals to decide whether they wish to undergo genetic testing and to help them assess and manage the results of genetic tests.

44. We will respect the right of each individual to decide whether or not to be informed of the results of genetic testing, and the resulting consequences will be respected.

45. Counselling will address the limitations of genetic testing as well as the potential benefits – patients should be advised that genetic testing does not, in all circumstances, provide certainty that the person tested or their offspring will develop particular diseases (conditions may be linked to multiple rather than single genes; environmental factors may also play a significant or dominant role in whether particular people develop diseases for which they may have genetic susceptibility).

Gene therapy

46. We will not undertake somatic cell gene therapy unless the proposal has been reviewed and approved in accordance with NHMRC guidelines. This requires consideration by the relevant Human Research Ethics Committee, the NHMRC's Gene and Related Therapies Research Advisory Panel, the Therapeutics Goods Administration and where relevant the Gene Technology Regulator.

Cloning and related technologies

47. We will comply with the *Gene Technology Act 2000* (Cth)[17], the *Gene Technology Act 2001* (Qld) and the *Gene Technology Regulation 2002* (Qld). We will also comply with the *Research Involving Human Embryos and Prohibition of Human Cloning Act 2003* (Qld) which bans human cloning, germ line gene therapy and ensures that research involving human embryos is strictly regulated.

Xenotransplantation

48. We acknowledge that concerns exist about the safety and efficacy of xenotransplantation (for example, the risk of animal retroviruses being transmitted to humans through xenotransplants).

49. We will abide by the NHMRC's decisions on issues surrounding xenotransplantation including the five year ban (until 2010) on conducting human clinical trials involving animal-to-human whole organ transplants.

50. We will only use animals in xenotransplantation research if suitable alternative therapies are not available. We will make every effort to keep the number of animals used in xenotransplantation research to a minimum and to ensure that these animals are provided with as high a quality of life as possible.

51. We note that research proposals involving xenotransplantation must be considered under arrangements administered by the NHMRC and that the NHMRC requires all research proposals involving xenotransplantation to be referred to the Gene and Related Therapies Research Advisory Panel (GTRAP) for scientific, medical and technical advice in the formulation and ethical review of the research. We also note that no Human Research Ethics Committee should approve any research proposal involving xenotransplantation without first seeking this advice.

[16] Article 2, *Universal Declaration on the Human Genome and Human Rights* (1997).
[17] Including the principles under the Gene Technology Ethic Committee *Draft National Framework for the Development of Ethical Principles in Gene Technology January 2006.*

Appendix One: Key steps in managing conflicts of interest

Point 5 under the Section *Integrity of Research and Product Testing* requires that biotechnology organisations establish systems to ensure that conflicts or potential conflicts of interest are disclosed and that reasonable steps are taken to address and resolve any conflict. These steps include:

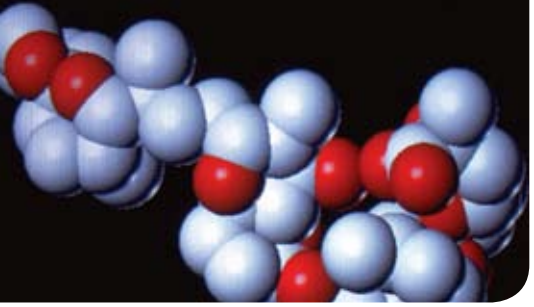
- Requiring staff[19] to disclose possible conflicts of interest.
- Requiring staff to disclose their pecuniary interests (including any business associations, shareholdings, sponsorships, donations, payments or fees).
- In particular cases:
  - determining whether a conflict or perceived conflict of interest exists that might call into question the integrity of the work; or
  - where appropriate, directing or advising a staff member to cease involvement in the work or to divest him or herself of external interests that are seen as incompatible with the integrity of the work; or
  - determining that a conflict (or perceived conflict) of interest is acceptable or unavoidable in the circumstances, is not detrimental to the integrity of the work, and is appropriately disclosed.

In cases where a conflict of interest exists or may exist, or where the circumstances could give rise to a reasonable perception of conflict, the biotechnology organisation should disclose the circumstances to relevant authorities having oversight of the activity concerned. The relevant authorities include:

- The ethics committee responsible for approval and/or monitoring of biotechnology activities within the organisation[20], where the circumstances relate to a matter or matters for which the committee has responsibility.
- An external research funding institution, where the circumstances relate to an activity funded, or proposed to be funded, by the institution.
- A regulatory authority where the circumstances relate to scientific advice or assessments that could be used by the authority to approve or monitor research or product release.
- An editor or producer of a professional journal, publication or media report, where the circumstances relate to scientific advice or assessments proposed for reporting in the journal, publication or media report.
- An advisory board or government authority where the circumstances relate to the provision of scientific advice provided to the board or authority (for example, where a member of our organisation is engaged or appointed to provide scientific advice on biotechnology matters in relation to which he or she may have, or may be seen to have, a beneficial interest).
- The organisation's financial administrator, where biotechnology products or services are purchased, or are being considered for purchase, from an external source in relation to which the purchasing officer has, or may have, a beneficial interest.

As a general rule, biotechnology organisations should disclose to relevant authorities all funding sources associated with research activities (irrespective of whether a conflict of interest may exist or is perceived to exist).

[19] "staff" includes management.
[20] Such committees include the relevant Institutional Biosafety Committee; the Animal Ethics Committee and the Human Research Ethics Committee. See Part III, paragraphs 9, 13 and 50 for an outline of these committees.



Glossary and Abbreviations

Biodiscovery
Biodiscovery has the meaning given in the *Biodiscovery Act 2004* (Qld) and includes the analysis of molecular, biochemical or genetic information about native biological resources for the purpose of commercialising the material.[21]

Biotechnology
Biotechnology is formally defined as the science of using living things, and components of living things, to produce goods and services. It involves manipulating and modifying organisms, often at the molecular level.

Practically, modern biotechnology includes techniques ranging from chemistry through molecular and cellular biology, biochemistry and immunology to biological applications of information technology and the development of medical instrumentation. Its applications span health, agriculture, industry and the environment.[22]

Cloning
The process of producing genetically identical organisms through various techniques, including culture of specific cells, artificial division of a single embryo, or cell nuclear transfer, that is, transferring the nucleus of a somatic cell into an oocyte (the mature female germ cell or egg) from which the nucleus has been removed.

Coexistence
Coexistence is defined as the ability to grow and manage along the supply chain both genetically modified and non-genetically modified or traditional crops in a way that avoids unwanted mixing and delivers products below predetermined market specification or thresholds.[23]

Culture
The growing of micro-organisms, tissue cells, or other living matter in a specially prepared nutrient medium (an intervening substance through which something else is transmitted or carried on).

Gene
A sequence of DNA, located on a chromosome, which codes for the synthesis of a specific protein or has a specific regulatory function.[24]

Gene technology research
Study involving the manipulation, modification and transfer of genes or segments of DNA or RNA.

Gene therapy
Treating or preventing genetic diseases by changing the expression of a patient's genes through the introduction of DNA or RNA into the patient's cells.

Genetic characteristic
A trait (distinguishing feature) of an organism determined by genetic inheritance.

Genetic inheritance
The acquiring of a set of physical or behavioural characteristics from a parent

Genetic modification
Any process altering the genetic material of living organisms.[25] This process allows genes to be isolated, amplified and transported into new locations, even between species, to effect desired characteristics in organisms. Examples include the duplication, insertion, or deletion of genes from another species, in situ in either microbes, plants or animals (humans included). Where this is done in humans, it is gene therapy, and only human genes are used.

Genetically modified food
A food produced using gene technology as 'a food which has been derived or developed from an organism which has been modified by gene technology'. This definition does not include a food derived from an animal or other organism which has been fed GM feed, unless the animal or organism itself is a product of gene technology.[26]

Genetically modified organism (GMO)
An organism (plant, animal, bacteria or virus) that has had its genetic material altered either by duplication, insertion or deletion of one or more new genes, or by changing the activities of an existing gene.[27]

[21] *Biodiscovery Act 2004* (Qld)
[22] Queensland Government *Queensland Biotechnology Strategic Plan 2005-2015: Biotechnology- Setting New Horizons*
[23] Queensland Government *Developing strategies for GM and non-GM crops in Queensland – A framework for co-existence.*
[24] Biotechnology Australia - Glossary of Terms (www.biotechnology.gov.au)
[25] Biotechnology Australia - Glossary of Terms (www.biotechnology.gov.au)
[26] Australian Food Standards Code Standard 1.5.2
[27] ibid

Genetic testing

Genetic testing has considerable potential in health care as a means of identifying individuals' genetic make-up, and enabling early prevention strategies to be targeted at persons or offspring most at risk of genetically determined diseases.

Genetically modified crops

Modifying the genetic code of agricultural crops to produce improved characteristics such as pest and disease resistance, drought and salt tolerance, higher yields or greater nutritional value.

Somatic cell

Any cell in a multicellular organism except a sperm or egg cell.

Xenotransplantation

The term used to describe any procedure that involves the transplantation of live cells, tissues, or organs from one species is to another, including animal to human transplantation (for example, from pigs to humans – animal-to-human transplantation).[28] Xenotransplantation includes:

- animal to human whole organ transplants
- animal cellular therapies – are procedures in which animal cells are transplanted or implanted into a human patient to compensate for deficient functioning of the patient's own cells (for example, pancreatic islet cells to treat people with diabetes, or brain cells to treat people with Parkinson's Disease) and
- animal external therapies – are a range of procedures involving contact between human and animal cells or tissues outside the body of the patient (for example, cells or fluids from the patient are perfused through animal cells and returned to the patient).

Abbreviations

AEC	Animal Ethics Committee
AHEC	Australian Health Ethics Committee
ARC	Australian Research Council
CRC	Cooperative Research Centre
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DNA	Deoxyribonucleic Acid
FSANZ	Food Standards Australia New Zealand
GM	Genetically Modified
GMO	Genetically Modified Organism
GTRAP	Gene and Related Therapies Research Advisory Panel
HREC	Human Research Ethics Committee
IBC	Institutional Biosafety Committee
NHMRC	National Health and Medical Research Council
OGTR	Office of the Gene Technology Regulator
RNA	Ribonucleic Acid

[28] Biotechnology Australia - Glossary of Terms (www.biotechnology.gov.au)

HEALTH PROFESSIONS COUNCIL OF SOUTH AFRICA

GUIDELINES FOR GOOD PRACTICE
IN THE HEALTH CARE PROFESSIONS

GENERAL ETHICAL GUIDELINES FOR BIOTECHNOLOGY RESEARCH IN SOUTH AFRICA

BOOKLET 14

PRETORIA
MAY 2008

Health Professions Council of South Africa
Post Office Box 205
Pretoria 0001

Telephone: (012) 338 9300
Fax: (012) 328 4863

E-mail: hpcsa@hpcsa.co.za

Website: http://www.hpcsa.co.za

THE SPIRIT OF PROFESSIONAL GUIDELINES

Practising as a healthcare professional is based upon a relationship of mutual trust between patients and healthcare practitioners. The term "profession" means "a dedication, promise or commitment publicly made".[1] To be a good healthcare professional requires a life-long commitment to sound professional and ethical practices and an overriding dedication to the interests of one's fellow human beings and society. In essence, practice as a healthcare professional is a moral enterprise. In this spirit, the Health Professions Council of South Africa presents the following ethical guidelines.

[Note: The term "healthcare practitioner" in these guidelines refers to persons registered with the HPCSA].

[1] Pellegrino, ED. Medical professionalism: Can it, should it survive? *J Am Board Fam Pract* 2000; **13**(2):147-149 (quotation on p. 148).

PREAMBLE

This guideline booklet was developed by Professor A Dhai, Dr N Msomi and Professor DJ McQuoid-Mason with funding from LIFE*lab* – EcoBio Regional Innovation Centre, Department of Science and Technology.

The Health Professions Council of South Africa adopted the Ethical Guidelines for Biotechnology Research at its meeting in November 2005 as its guideline document on biotechnology research as annexed below.

CODE OF ETHICAL PRACTICE FOR MEDICAL BIOTECHNOLOGY RESEARCH IN SOUTH AFRICA

1. THE IMPORTANCE OF ETHICS

1.1 Introduction

The field of medical science and biotechnology is constantly changing and advancing and new ethical issues emerge regularly. Therefore, this guideline is intended as a live document which is subject to continuous change and amendment in order to address areas of new ethical concerns.

The rapid progress of modern biotechnology has presented a number of new and unique ethical and social challenges within the context of human medical science. Research in medical biotechnology has led to increased knowledge of disease, acceleration of the healing process, improved drug treatment for infectious diseases and hope for the struggle against incurable diseases such as HIV/AIDS, Parkinson's and Alzheimer's. Medical biotechnology promises major advances in human health and therefore, any limitations on the right to freedom of scientific research should be for significant reasons only, and as least restrictive as possible, so as not to impede scientific wisdom and prevent damage to the scientific undertaking.[2] At the same time a duty exists to ensure that research in this area of biotechnology is conducted in ethically acceptable ways. A balance needs to be struck between recognising the potential benefits which biotechnology research offers to individuals and the community as a whole, and the duty to ensure that research in this area is conducted ethically.

South Africa provides a unique research environment due to its sound infrastructure, well equipped research institutions, skilled researchers and surfeit of emerging and re-emerging disease trends.[3] However, a large part of the South African population, consists of vulnerable groups and poor populations with low levels of education, who accept authority without question and who are easily influenced.[4] This poses new ethical dilemmas which have to be addressed. The vulnerability and inequity, coupled with the unique research environment in South Africa, emphasises the need for an ethical guideline governing biotechnology research which ensures that research is conducted ethically and that vulnerable persons and communities are not exploited.[5] For the purpose of this guideline, it is important to define the concept of a 'vulnerable group' and to answer the question of how vulnerability is defined in research.

Vulnerable persons are those who may have 'insufficient power, intelligence, education, resources, strength', or other attributes which make them capable of protecting their own interests.[6] Vulnerable communities can further be defined as those communities which may have some or all of the following characteristics:

- Limited Economic Development;
- Inadequate Protection of Human Rights;
- Discrimination on the basis of health status;
- Inadequate understanding of scientific research;

[2] A Dhai, J Moodley, D J McQuoid-Mason & C Rodeck 'Ethical and Legal Controversies in Cloning for Biomedical Research – A South African Perspective' (2004) *SAMJ* Vol 94, No 11, 909.
[3] Department of Health South Africa *Ethics in Health Research: Principles, Structures and Processes* (2004).
[4] Ibid.
[5] Ibid.
[6] Council for International Organisations of Medical Sciences *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002).

- Limited availability of healthcare and treatment options;
- Limited availability of individuals in the community to provide informed consent.[7]

The South African Ethics in Health Research Guidelines support these definitions and state:

Caution must be exercised before undertaking research involving participants in such communities.

Since the majorityof South African citizens fall within the category of 'vulnerable persons', it is crucial that this ethical guideline should not only protect the rights of individual research participants, but should also ensure that research on potentially vulnerable participants is conducted ethically.

Some aspects of modern biotechnology also give rise to ethical dilemmas due to the various moral, cultural, religious, family and personal factors involved – these concerns must also be addressed. This ethical guideline recognises the injustices of South Africa in the past and embraces national and international trends and views in light of the Constitution of South Africa Act 108 of 1996: human dignity, the achievement of equality and the advancement of human rights and freedoms.

1.2 Key texts

The ethical principles and guidelines, contained in the National and International texts and sources set out below, have been combined and extensively utilised in compiling this guideline.

The following South African key texts have directed the development of these guidelines and must be acknowledged:

- The Constitution of the Republic of South Africa;[8]
- The Department of Health – Ethics in Health Research: Principles, Structures and Processes;
- Guidelines on Ethics for Medical Research in South Africa (MRC).

The following key International texts and sources have influenced the development of these guidelines and must be acknowledged:

- The Code of Ethical Practice for Biotechnology in Queensland (issued by the Queensland Government) which became operational on 1 September 2001;
- The Nuffield Council on Bioethics Guidelines;
- Belmont Report, 1973;
- The Cartagena Protocol on Biosafety;
- The Declaration of Helsinki, 2000;
- The Nuremberg Code, 1949;

[7] Joint United Nations Programme on HIV/AIDS (UNAIDS), website available at www.unaids.org cf: Department of Health South Africa *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa* (2004) 27.

[8] Act 108 of 1996

- The Council for International Organizations of Medical Sciences (CIOMS) Guidelines;
- Commonwealth of Australia, NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (June 1999);
- Commonwealth of Australia, Australian Health Ethics Committee (endorsed by the NHMRC) *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research* (September 2004);
- Joint United Nations Programme on HIV/AIDS (UNAIDS);
- The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS).

1.3 Scope of the guidelines

In order to develop a comprehensive ethical framework that would guide researchers in the field of medical biotechnology and human health, it would be important, as a first step, to determine the scope of the subject matter one wishes to set ethical standards for.

This guideline only addresses ethical issues with regard to 'biotechnology research'. The term 'research' covers a broad spectrum of activities and can be defined as the 'systematic search or enquiry for knowledge'.[9] In South Africa, a distinction exists between 'therapeutic' and 'non-therapeutic research'. The Declaration of Helsinki defines therapeutic research as research which is potentially beneficial to the research participant whereas non-therapeutic research is not intended to be beneficial to the actual participant but valuable to the development of health solutions and generalisable medical and scientific knowledge.

Biotechnology is a broad term for a wide range of technologies which use living organisms, biochemistries or synthetic DNA to make or modify products, improve plants or animals, or develop micro-organisms for specific uses. Biotechnologies have many different applications in medicine, agriculture and food production, horticulture, industry and the environment.

The term 'biotechnology' is an ambiguous term and the fact that the field of biotechnology is extensive and diverse, further adds to the complexity and difficulty of setting an ethical standard for research in the field, since it encompasses a multitude of ethical challenges. Researchers in the biotechnology industry face challenges unlike researchers in other sectors. Unlike most other industries, advances and research in the biotechnology industry are often front page news and has to face intense scrutiny by press, academics, government and the public. As biotechnology is a newly emerging field, a further challenge facing the industry is the lack of historical precedence in the sector to provide guidance for the safe and ethical development of the technology.

Some biotechnologies have been around for many years. For instance, the use of yeast and bacteria in the making of bread, wine, beer and cheese by means of conventional fermentation processes is a biotechnology which has been in common practice for centuries. Traditional plant and animal breeding techniques also form part of biotechnology.

[9] Katzenellenbogen, Gear & Tollman (1997) cf: Department of Health South Africa *Ethics in Health Research, Principles, Structures and Processes* (2004).

However, the biotechnologies which are the focus of this ethical code are the more modern kind which take the above techniques a step further and makes use of genetic engineering to adapt the properties of bacteria, plants and animals by directly intervening in the information carrier that is the basis for all properties of each organism: the DNA. These new techniques provide better understanding of, and potentially more control over, living processes at the level of individual cells and genes and offer a variety of new and practical applications in agriculture, medicine and industry. However, these new techniques raise safety issues and important ethical concerns.

Examples of these new controversial techniques are gene mapping, DNA sequencing, diagnostics, genetic modification and cloning. These are briefly discussed below.

1.3.1 Gene Mapping, DNA Sequencing and Diagnostics

As a group these above-mentioned techniques involve identifying and understanding the functions of genetic information and programming, and identifying individual variations in genetic programming for medical or other scientific purposes. Knowledge obtained from these research practices can assist to facilitate better understanding of disease or disease susceptibility, and to design new therapeutic treatments and other processes and products. These techniques include:

- Gene mapping which involves locating the position of genes on a chromosome;
- Gene sequencing which involves the deciphering of the genetic code by finding the ordering of building block molecules within genes;
- Functional genomics which entails searching for changes in DNA sequences (mutations) in inbred experimental animals, such as laboratory mice in order to identify the functions of particular genes; and
- Diagnostics which involves the development and use of test kits and probes to identify particular genetic characteristics in humans, plants and animals. In the healthcare environment, diagnostic tests are being developed and used to detect an individual's genetic predisposition to particular diseases.

1.3.2 Genetic Modification

Genetic modification is the process of allowing genes to be isolated, amplified and transported into new locations, even between species, to obtain desired characteristics in certain target organisms. It is used in a variety of applications including:

- The production of pharmaceuticals (such as human insulin for diabetics) and vaccines (for example, for hepatitis B);
- Gene therapy which involves the treatment or prevention of genetic diseases by changing the expression of a patient's genes through the introduction of DNA or RNA into the patient's cells;

1.3.3 Cloning

Cloning is the process of producing genetically identical organisms through various techniques, including culture of specific cells, artificial division of a single embryo, or cell nuclear transfer where the nucleus of a somatic cell is transferred into an oocyte (the mature female germ cell or egg) from which the nucleus has been removed.

Cloned animals can be used in agriculture to breed animals with improved characteristics. In addition, they can be used to model human diseases and to manufacture pharmaceuticals for medical healthcare needs.

In medical research, cloning may also involve the artificial production of particular tissues or organs from embryonic or adult (e.g. bone marrow) cells for the repair of diseased or damaged tissue.

1.4 Ethics approval and Biotechnology Research

In biotechnology research, the usual ethical principles applicable to health research involving animals and human participants must be observed and such research must be scientifically sound.

Any research project should be subject to the review of a South African based Ethics Committee who must review the ethical and scientific rigor of the proposed research. In the context of health research, the National Health Act[10] provides for the establishment of Health Research Ethics committees who must approve any proposed research activity.[11]

The objects of Research Ethics Committees are to:

- Maintain ethical standards of practice in research;
- Protect research participants and investigators from harm or exploitation;
- Preserve the research participant's rights which take preference over society's rights; and
- Provide assurance to the public that research is conducted ethically.

In the context of the genetic modification of organisms, no specific Research Ethics Committee exists, however the Genetically Modified Organisms Act[12] provides for the establishment of an Executive Council to which applications for research involving GMO's must be submitted. The Executive Council is assisted in their decision-making by the Advisory Committee, which consists of scientists and reviewers, as well as information obtained from other countries. No activities involving GMO's[13], including any research, may be commenced until the Executive Council has approved such activity and issued the required permit.

[10] Act 61 of 2003.
[11] Chapter 9.
[12] Act 15 of 1997, sections 3 and 5.
[13] Academic research, use in contained facilities, trials, general commercial use, imports, exports and in-transit consignments.

2. GUIDING PRINCIPLES

This guideline addresses the ethics of research in South Africa to ensure compliance with the basic ethical values of beneficence, non-maleficence, justice and respect for persons. Furthermore, the guideline aims to identify good, desirable and acceptable conduct in research which promotes the welfare and rights of research participants.

Any research, including biotechnology research must conform to the following ethical principles and values:

2.1 Integrity

Researchers must always act with honesty and respect for the truth.

2.2 Autonomy/Respect for persons

Patients, participants and research subjects must be treated with respect for their individual autonomy, freedom of choice, dignity and human rights. Informed consent is a vital element to respecting the right to individual autonomy.

2.3 Beneficence

Researchers must always act in the best interests of the patient/research participant and make efforts to secure their well-being.

2.4 Non-maleficence

The “do no harm” principle applies to biotechnology research and entails refraining from doing harm and attempting to maximise possible benefits and minimising possible harms.

2.5 Justice/Fairness

In research endeavours, researchers must attempt to address past inequities, recognising wider community interests beyond merely the interests of the individual, organisation or corporation, providing redress for the vulnerable and promoting equitable access to resources. This principle can also be described as necessitating an equal distribution of the risks and benefits of research between communities.

2.6 Ethical Duties

2.6.1 Respect for the Law and system of government

There must be compliance with the Constitution of the Republic of South Africa[14] and all relevant South African legislation and standards.

2.6.2 Relevance

[14] Act 108 of 1996.

Biotechnology researchers in South Africa have an ethical responsibility to ensure that their research is relevant. Only biotechnology activities which have the potential, in the South African and African context to improve human health and quality of life, support for the environment and promotion of sustainable agriculture and industry must be pursued. This limits the scope for biotechnology research to areas where the results could have a potential positive impact on human health, the environment and agriculture.

2.6.3 Investigator Competence

Only investigators who are competent and appropriately and suitably qualified in the necessary field of biotechnology should conduct the research. Where delegation of research is necessary, the principal investigator should only delegate to individuals who possess the necessary skills and experience.[15] Researchers must at all times endeavour to achieve the highest level of scientific quality in their research.

When assessing the competence and suitability of the researcher to conduct the specific research the following attributes must be taken into account:

- Technical and research competence;
- Educational background and qualifications;
- Certification;
- Knowledge and experience in the required field;
- Honesty and Integrity;
- Fairness;
- The researcher's sensitivity to identify an ethical issue; and
- The ability to act responsibly and appropriately when faced with an ethically challenging situation.

A technically competent researcher must be empathetic and compassionate and these characteristics will best be maintained in a good clinical and research environment that provides appropriate research mentoring.

Researchers must never misuse their positions or knowledge for personal power or gain.

2.6.4 Informed Consent

It is necessary to obtain the informed consent from the research participant prior to commencing research.[16] This requirement is based on the fundamental moral duty that we do not act against the wishes of a person and that human dignity and integrity should be respected. This is further required in terms of section 12 (2) (c) of the Constitution and section 71 of the National Health Act[17] which states that research or experimentation on a living person may only be conducted with the informed consent of that person. Previously, Research Ethics Committees had to rely on ethical guidelines and to some extent, Constitutional and common law for ethical guidance regarding research on human subjects. The National Health Act can be seen as the first attempt by the

[15] South African Health Info 'Ethics in Health Research' available at www.sahealthinfo.org/ethics/ethicsconduct.htm (site last visited on 03/06/05).
[16] In addition International guidelines on research ethics including the World Medical Association's *Declaration of Helsinki* and the Council for International Organisations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* stress the importance of obtaining ethically and legally valid consent in research.
[17] Act 61 of 2003.

legislature to address some ethical concerns raised by using human participants, including children, in research and specific emphasis is placed on the issue of informed consent.[18]

The preferred manner of recording consent is in both written and verbal form. Where the participant is not literate, the consent must be obtained in the presence of a literate witness who must confirm in writing that the consent obtained was in fact informed in nature. This means that the research participant was informed of all information relevant to his/her participation, including the risks and benefits of the proposed research and understood all the risks and benefits of such research. Unforeseeable risks obviously cannot be foreseen, but participants must be told the nature and extent of all foreseeable risks or discomfort associated with the research. This includes financial risks attendant on participation. The person must also have been able to give consent voluntarily without any form of coercion or undue influence.

Research Ethics Committees must ensure that informed consent procedures are followed.

The four main requirements for informed consent are:

(a) Disclosure;
(b) Understanding or appreciation;
(c) Voluntariness; and
(d) Capacity to consent.

2.6.4.1 Disclosure

Disclosure relates to information which must be supplied to a research participant prior to obtaining consent to participation in order for such consent to be informed. Participants must be made aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator may terminate participation and be informed of the availability of peer counseling to assist them in making an informed choice.

Disclosures made to prospective participants must be detailed and comprehensive, made in the appropriate language[19] and in a manner that facilitates understanding. The researcher should adopt a non-threatening approach that invites interaction and questions from the participant. Where possible, researchers should make use of an environment where the potential participant feels comfortable and not intimidated.

In the event of significant changes in the conditions or procedures of the research, or if new information comes to light which may impact on participants continuing with the research, new informed consent[20] must be obtained from such participant.

[18] A Strode, C Grant, C Slack & M Mushariwa 'How well does South Africa's Health Act Regulate Research Involving Children' *SAMJ* (2005) Vol 95 No 4 at 265.
[19] In a language in which the participant is fluent and which s/he chooses to converse in.
[20] In obtaining the new informed consent, disclosure must be made of any new conditions, procedures or information.

The following list is a concise summary of essential information that must be disclosed to biotechnology research participants in order to facilitate informed consent. Participants must be informed of all relevant information which may impact on their decision to participate in the research, including the following:

(a) That they are participating in research and that participation is voluntary;

(b) What the aim of the research is and the anticipated time period of his/her involvement in the research;

(c) The research and experimental procedures to which s/he will be subjected;

(d) Any and all responsibilities which s/he will have if they consent to participate in the research;

(e) Any and all risks, dangers and/or complications that may result from, or be inherent in, the research. This includes the possibility of unforeseen risks, dangers and complications that may result from such research;

(f) The benefits to him/herself or others, both during and after the research;

(g) What will happen in the event of him/her being injured in any way during participation in the research, including whether compensation will be given in research related injuries (participants must also be told who to contact in the event of such injury);

(h) That they have a right to be informed of relevant new findings related to the research;

(i) That s/he may at any stage of the project withdraw his or her consent to participate without any disadvantage to him or herself;

(j) The consequences of their withdrawal from research;

(k) Whether the researcher is allowed to terminate participation and the circumstances which may lead to such termination;

(l) That peer counseling is available to assist him/her in making an informed choice;

(m) The extent to which confidentiality will be maintained and that the sponsors of the study and regulatory bodies[21] will be permitted to inspect research records;

(n) Where during the course of research, information comes to light which the participant may have a legal duty to disclose to a third party[22], the researcher may have a duty to disclose such information to the third party, should the participant refuse/fail to do so;

[21] Such as the Medical Control Council (MCC) and applicable Research Ethics Committees (REC's).

[22] For example where disclosure is required in terms of a life insurance policy or where withholding the information may endanger a third party.

(o) Whether the research has been approved by an accredited research ethics committee and that the contact details of such research ethics committee representatives must be made available to the participant;

(p) The investigator's qualifications which make him/her suitable and competent to conduct the research;

(q) The investigator's contact details should the participant require additional information or suffer an adverse event;

(r) The possible research uses, direct or secondary, of the participants medical records and of biological specimens taken during the course of the research;

(s) Whether biological specimens collected during the research will be destroyed, stored[23], possible future use. Participants must be made aware that they have the right to decide about the future use of such specimens and that the specimens may not be used in any other or subsequent research unless the participant's informed consent has been obtained in writing for that specific research project;

(t) That the researcher may have a legal duty to breach confidentiality if, during the course of research, it is discovered that the participant has a notifiable disease.

2.6.4.2 Understanding or appreciation

Obtaining informed consent must be done in a manner which recognises the individuality of the specific participant by considering factors such as his/her age, maturity, intelligence, education and belief system. Merely reading out the contents of the consent form in a mechanical way will not suffice as satisfactory disclosure. The researcher must be completely certain and confident that all information disclosed to the participant was understood and that s/he appreciates all risks and benefits associated with the proposed research. The researcher must allow the participant to ask questions freely and must ensure that all questions are answered honestly and appropriately. In addition, the researcher must ensure that the participant is provided with sufficient opportunity to consider all the information prior to consenting.

In the South African context, researchers must pay particular attention to the vulnerability of potential research participants. Many vulnerable South African populations do not have access to primary, secondary or tertiary education, nor to adequate health care services which makes them particularly vulnerable to exploitation by researchers and research establishments. For this reason, details of the proposed research must be supplied to the participant in a manner which is easily understandable and which takes cognizance of the cultural background, language, customs and beliefs of the participant.

2.6.4.3

[23] Where such specimens will be stored, the participant must be informed of whether the stored specimen will be marked in an identifiable or anonymous form and what the implications for storage will be for the participant.

2.6.4.3 Voluntariness

Informed consent is only valid when it is obtained without dishonesty or misrepresentation. Any compulsion or undue influence on the part of the researcher will negate the consent given by the participant.

2.6.4.4 Capacity to consent

Consent must be given by someone who is legally and factually capable of consenting. In relation to competence to consent and proxy consent, two broad categories of research participants must be recognised: Adults and Minors.

2.6.4.4.1 Adults

The general rule is that sane and sober adults have the capacity to give valid consent to participation in research. However, the following categories of adults are exceptions to the general rule since consent obtained from these categories may be compromised. In some instances the consent given may be invalid or special or additional considerations must be addressed for such consent to become valid.

The mentally ill or handicapped

The Mental Health Care Act No. 17 of 2002 provides for consent to clinical interventions, on mentally ill patients which are institutionalised.

In the case of therapeutic research on a mentally ill or defective person who is incapable of consenting, it is permissible to obtain proxy consent. However, proxy consent is only permissible where the proposed research is directly or indirectly relevant to the patient's mental illness or defect. In addition, the assent of the mentally ill person must be obtained, provided that such patient is able to comprehend the issues involved.

As a general rule, participation of a mentally ill or handicapped person in non-therapeutic research is not allowed. However, certain exceptions exist where non-therapeutic research is permitted, provided that proxy consent is obtained. The exceptions are:

- Observational research of a non-invasive nature since the incapacitated person is not placed at risk and there is no interference with his/her integrity. The research must entail no more than minimal risk or discomfort;
- Observational research of a non-invasive nature provided that no more than minimal risk is foreseeable or known from routine medical practice and distress and discomfort must be minimal.

With regard to non-therapeutic research, the following requirements must be met in addition to the above:

- The research must pertain directly or indirectly to the mental illness or defect from which the person suffers;
- The assent of the participant must be sought and adequate consideration given to his or her wishes expressed in any advanced directives. Any objection by the incapacitated person would be decisive and the research will not be permitted;
- The research involved must significantly benefit persons of the same category as the research participant;
- The research will not be permitted if the same scientific results can be obtained by other methods or by research on persons who do not belong to the same category as the proposed mentally ill or incapacitated participant.

Elderly

The general rule is that, in the absence of any indication to the contrary, elderly persons are assumed to be competent to consent to research. Consideration should however be given to the likelihood of factors such as:

- Possible mental deterioration;
- The ability to comprehend; and
- Their dependence and vulnerability.

Pregnant Women

It is generally assumed that pregnant women are competent to consent to research. However, certain circumstances e.g. active labour, may compromise their decision. As a general rule, the father of the unborn child should be included in the decision making process where possible.

Unconscious Patients

Unconscious patients are incapable of consenting to research. Therapeutic research on unconscious patients would however be legally permissible where:

- there are no indications to the contrary;
- informed consent of a competent relative has been obtained.

The Dying

When determining the capacity of a dying person to consent to research, each situation will be assessed independently and on its own merit. The vulnerability and dependency of such participant must always be taken into account in any attempt to obtain their consent for research.

2.6.4.4.2 Minors and Children

Minors may participate in research only where their participation is indispensable to the research.[24] Furthermore, the research must never be contrary to the minor's best

[24] Department of Health South Africa *Ethics in Health Research: Principles, Structures and Processes* (2004) 21.

interests[25] and the aim of the research should investigate and focus on issues which are relevant specifically to children. It is important that the circumstances in which the research involving children is conducted must provide for the physical, emotional and psychological safety of the minor involved.[26]

The Constitution[27] and the Children's Act No. 38 of 2005, defines a child as a person under the age of 18 years. In terms of the Children's Act No. 38 of 2002, a person under the age of 18 years is a minor. Where a perhson on account of age is not capable of consenting to the proposed research procedure, proxy consent[28] must be procured.

Special guidelines must be followed for research on minors. The following terms are defined in the South African Department of Health Research Ethics Guidelines 2004 and are important definitions to review for determining proper research protocol on minors:[29]

- *Therapeutic Research* includes 'interventions that may hold out the prospect of direct health-related benefits for the participant'.
- *Non-therapeutic research* includes 'interventions that will not hold out the prospect of direct health-related benefits for the participants, but results may be produced that significantly contribute to generalisable knowledge about the participant's condition'.

The Children's Act outlines that:

- Minors 12 years or older are 'legally capable of consenting to medical treatment on themselves and their children'.
- Minors who are 12 years or older are 'legally capable of consenting to surgical operations upon themselves'.

Those minors who do not fit into these age criteria, must have the consent of a parent or legal guardian grant approval for medical treatment or surgical operations.

---

[25] The Children's Bill (available at www.childrenfirst.org.za/pdf/27January2004Bill.pdf) outlines key factors that must be considered when determining the "best interests of the child". These factors include:

- The child's age;
- Needs;
- Gender
- Background;
- Maturity and stage of development;
- Needs to protect the child from physical and psychological harm; and
- The opinion of the child.

[26] Commonwealth of Australia NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (1999) 25.

[27] Section 28 (3).

[28] Consent by a person who is legally authorised to act on behalf of the incompetent person.

[29] Department of Health South Africa *Ethics in Health Research: Principles, Structures and Processes* (2004) 21.

The National Health Act regulates consent in research. Section 71, while regulating on minors does not distinguish them into age categories. Rather, it looks at minors as one group and outlines requirements for 'therapeutic' and 'non-therapeutic' research.

According to the National Health Act:[30]

Therapeutic research on minors may only be conducted:

- If it is in the best interest of the minor;
- With the consent of the parent or guardian of the minor;
- If the minor is capable of understanding, with the consent of the minor.

Non-therapeutic research on minors can only be conducted:

- With the consent of the Minister of Health;
- With the consent of the parent or guardian of the minor;
- If the minor is capable of understanding, with the consent of the minor.

2.6.5 Privacy and Confidentiality

Privacy and confidentiality in the context of genetic research is discussed in chapter 13.2.2 and supplements the basic principles of privacy and confidentiality in research as discussed in this chapter. Please refer to this chapter.

The right to privacy is protected in section 14 of the Constitution and includes protection against the disclosure of private facts which were obtained during a relationship where confidentiality applied.[31] This right includes protection against the unwanted publication or disclosure of intimate personal information. Information regarding a research participant obtained during the course of research must be treated as confidential, irrespective the origin of such information.[32] The right to confidentiality is also recognised in section 14 of the National Health Act[33] which states that:

> (1) All information concerning a user, including information relating to his or her health status, treatment or stay in a health establishment, is confidential.

[30] Act 61 of 2003, section 71 (2).
[31] J de Waal, I Currie & G Erasmus *The Bill of Rights Handbook* 4ed (2001) 268.
[32] The origin could be from the medical or other records of the participant or from the research activity itself.
[33] Act 61 of 2003.

(2) Subject to section 15[34], no person may disclose any information contemplated in subsection (1) unless –

(a) The user consents to that disclosure in writing;

(b) A court order or any law requires that disclosure; or

(c) Non-disclosure of the information represents a serious threat to public health.

Furthermore, researchers have a duty to take precautions to preserve confidentiality by for example using codes in research records as a means to identify participants instead of using their real names.

Examples of measures aimed at protecting the privacy of research participants include:[35]

- **Potentially identifiable (coded) storage methods**

  Data may have identifiers removed and substituted with a code. However, the process is reversible since the code could be used to re-identify the person to whom the data relates.

- **De-identified storage method**

  This method ensures the utmost protection of confidential information. Normally the identifiers are removed permanently or the data has been de-identified permanently. The de-identified information cannot be retrieved and remains anonymous, ensuring confidentiality.

The general rule is that information about research participants may only be released to a third party if the participant, or someone legally capable of consenting on his or her behalf, consents thereto. However, there are exceptions to this general rule which are discussed in chapter 2.6.5.1 and 2.

The duty to respect and maintain privacy and confidentiality does not end at the conclusion of the specific research project. It extends to any subsequent use of the confidential information.[36]

2.6.5.1 Endangered third parties

[34] Section 15 provides that personal information regarding a user may be disclosed as is necessary for any legitimate purpose within the ordinary course and scope of his or her duties and where such disclosure is in the interest of the user.

[35] Department of Health *Ethics in Health Research: Principles, Structures and Processes* 34 – 35.

[36] It must be borne in mind that for any subsequent use, new informed consent must be obtained from the research participant.

Where, during the course of research, facts regarding a condition or factor affecting the participant comes to light, which poses a serious risk to a third party, the researcher may have a duty to disclose the existence of such fact to the third party. This is in accordance with the principle of beneficence. However, the researcher should only disclose in the event that the participant/patient refuses to do so. In the same vein the Health Profession's Council of South Africa has imposed an ethical duty on medical practitioners to make a disclosure to the sexual partner or spouse of their HIV positive patient, if the patient refuses to do so themselves.[37] Medical practitioners may be held legally liable for failing to disclose this information to the relevant third party.[38]

2.6.5.2 Notifiable diseases

Confidentiality may also be broken where legal exceptions apply and disclosure is required by law as it is an ethical duty to respect the law and system of government. This is the case where clinicians or researchers have a duty to disclose if it comes to light that the participant has a notifiable disease. Researchers must note that they have to inform the participant of this duty when obtaining informed consent.

[37] South African Medical and Dental Council (SAMDC) *Bulletin* (September 1989) 6 2.
[38] MA Dada & DJ McQuoid-Mason *Introduction to Medico-Legal Practice* (2001) 21.

3. THE ETHICS OF RESEARCH RELATED TO HEALTHCARE IN SOUTH AFRICA AS A DEVELOPING COUNTRY

3.1 Ethical Duties

At all times the four ethical duties which are crucial when research is carried out in developing countries must be adhered to. These are:

(a) The duty to show respect for persons;
(b) The duty to alleviate suffering;
(c) The duty to be sensitive to cultural differences and different cultural perspectives which individuals might bring to questions of health and healthcare;
(d) The duty not to exploit the vulnerable or weaker for own advantage.[39]

3.2 Informed Consent

Refer to chapter 2.6.4 of this guideline where the usual requirements for informed consent are discussed in full.

In South Africa, as a developing and multi-cultural country, the issue of informed consent is pertinent. Many people in different cultures are unfamiliar with or do not readily understand scientific concepts such as 'biotechnology'. The potential for abuse is great and regard must be had to the language, culture, traditions and education of the specific individual in order to ensure that the person fully understands all implications of the proposed treatment or research and that the consent obtained from such person is truly informed and voluntary.

In order to protect the vulnerability of many of the research populations, researchers should develop culturally appropriate ways to communicate information that is essential for observance of the usual standards required in the informed consent process.

3.3 Recognition and respect for different cultures, values and beliefs

When planning and conducting research there exists a duty to recognise and respect the importance of national and local cultures, social systems, values and beliefs of the people and communities that may be affected by such research.

3.4 Allocation of resources

As a developing country, South Africa has limited national resources to be allocated to biotechnology research. Subsequently, research must, as a first priority, be aimed at those technologies which have the potential to directly benefit South African health care and agriculture and address the needs of the South African population and sustainability of the environment. The pertinent issues of HIV/AIDS, Tuberculosis (TB), tropical

[39] Nuffield Council on Bioethics 'The Ethics of Research Related to Healthcare in Developing Countries' (2002).

diseases[40], malnutrition and other poverty related illnesses are examples of areas which biotechnology research and development should prioritise and address.

Furthermore, section 70 of the National Health Act[41] sets out certain health research priorities which the National Health Research Committee must consider when identifying areas where the Minister should prioritise allocating resources to. These considerations are:

- the burden of disease;
- the cost effectiveness of interventions aimed at reducing the burden of disease;
- the availability of human and institutional resources for the implementation of an intervention at the level closest to the effected communities;
- the health needs of vulnerable groups such as women, older persons, children and people with disabilities;
- the health needs of communities.

[40] Such as malaria, African sleeping sickness, dengue fever, river blindness, elephantiasis, leishmaniasis, Chagas disease, schistosomiasis etc.
[41] Act 61 of 2003.

4. INTEGRITY OF RESEARCH AND PRODUCT TESTING

The Constitutional Right to freedom of research set out in section 16 (1) (d) of the Constitution must be exercised in a manner that will protect the scientific, intellectual and professional integrity of researchers and research establishments.

All research and product testing must be performed by appropriately qualified persons to optimal scientific standards with full regard to the relevant facts and data.

Accurate and comprehensive records of research and product testing must be kept and must comply with the appropriate regulatory authorities. Negative as well as positive results must be reported.

Conflicts of interest which may call into question the integrity of research, product trials, or other biotechnology activities must be avoided. Systems must be established to ensure that all conflicts, or potential conflicts of interest, are disclosed and that reasonable steps are taken to address and resolve the conflict.

5. CARE AND PROTECTION OF RESEARCH STAFF

Adequate safety measures must be employed within biotechnology organisations to ensure the health and safety of staff engaged in biotechnology activities and research. All staff must be properly trained in safety procedures.

Furthermore the Occupational Health and Safety Act[42] places a duty on employers to ensure the health and safety of their employees and to take measures to protect them against the hazards to health and safety arising out of, or in connection with, the activities such employees are involved in. The appropriate Research Ethics Committee should stress the importance of protecting the safety and welfare of research staff.

The primary investigator in the research should devise guidelines and apply safety rules for the proper handling of all hazardous materials.[43] In this regard, the Hazardous Substances Act[44] must be consulted.

Employers have a duty to comply with the relevant requirements of the Basic Conditions of Employment Act[45], Labour Relations Act[46], Compensation for Occupational Injuries and Diseases Act[47] and the Occupational Health and Safety Act[48]. All relevant South African and institutional standards governing laboratory safety must be adhered to in order to ensure the welfare of researchers and laboratory personnel.

[42] Act 85 of 1993.
[43] South African Health Info 'Ethics in Health Research' available at www.sahealthinfo.org/ethics/ethicsconduct.htm (site last visited on 06/06/2005).
[44] Act 15 of 1973.
[45] Act 75 of 1997.
[46] Act 66 of 1995.
[47] Act 130 of 1993.
[48] Act 85 of 1993.

6. CARE AND PROTECTION OF ANIMALS

Animal testing raises many contentious issues. Researchers must at all times ask the question: 'How valuable is the knowledge sought and how necessary is the use of animals to obtain the knowledge?'

Sentient animals must not be used in research, nor research conducted on such animals, unless the potential benefit of the technology being researched outweighs the moral and ethical concerns raised by utilising such animals as a means to an end.

6.1 Medical Research Council Guidelines on the use of animals in research and training

The guidelines laid down by the Medical Research Council (MRC) in 'Guidelines of Ethics for Medical Research: Use of Animals in Research and Training' must be observed. This is only an extract and the full text should be consulted and is available at www.mrc.ac.za.

6.1.1 General Policy

The following are the main ethical points recognised by the MRC which must be adhered to:

- It is preferable to only subscribe to studies which promise to contribute to the understanding of biology and environmental principles and to the acquisition of knowledge that can reasonably be expected to benefit humans, animals or the environment.
- All vertebrate animals are protected by law in South Africa[49] and it may be an offence to kill or interfere with the well-being of an animal for scientific or educational purposes without justification which is ratified by a formal process of ethical review.
- Animals may only be used when the researcher's best effort to find a non-sentient alternative has been unsuccessful.
- Optimal standards of animal health and care must be observed to provide good quality results which enhance credibility and reproducibility.
- The three "R" principles of replacement, reduction and refinement[50] must be adhered to when conducting and planning animal studies. These uphold the principles and practice of utilising the most humane methods on the smallest number of animals that will permit valid scientific information to be required.
- The use of animals in science depends on maintaining public confidence in the mechanisms and processes used to ensure that animal experiments are justified and humane.
- Laboratory animals are protected by law in South Africa and accordingly their use in education, testing and research purposes must be justified.

[49] Animal Protection Act 71 of 1962.
[50] As discussed in chapter 6.1.2.4 of this guideline.

6.1.2 Ethical Principles

6.1.2.1 Moral philosophy

It is accepted that sentient, non-human animals have the capacity to experience a range of physical sensations and emotions and are therefore subjects of moral concern.

6.1.2.2 Utilitarian ethic

The use of laboratory animals as research subjects in bio-medical science must be justified by the assurance that the potential benefit to either humans, animals and/or the environment outweighs the potential harm to the animal subjects. Each proposed experiment must therefore be supported by an ethical analysis stating the harm to animals/benefit to humans, animals or the environment. This ethical analysis must determine that more utility (good) than disutility (harm) will probably result from the proposed experiment. The end result should therefore be that the overall likely benefit will outweigh the potential harm to the animals.

6.1.2.3 Human obligations towards laboratory animals

Laboratory animals should be able to live, grow, reproduce and interact under conditions and circumstances in which their species' specific needs are met, as far as possible. Special consideration should be given to the needs of social animals in this regard and to animals which have adapted to special circumstances or environments e.g. nocturnal animals and marine animals.

6.1.2.4 Humaneness and the principles of humane experimental techniques

Experimental procedures which may expose animals or cause conditions such as hunger, thirst, injury, disease, discomfort, fear, distress, deprivation or pain must be kept to a minimum. The definition of humaneness is the practice to reduce the sum total of these conditions to a minimum or, preferably, to eliminate them altogether, by applying the 'three R' principles of Russell and Burch as follows:

- **Replacement**

Replacement of sentient animals with non-sentient research models or systems in order to eliminate the use of animals that can experience unpleasant sensations.

- **Reduction**

Reduction of the numbers of animals in experiments by design strategies that facilitate the use of the smallest number that will allow valid information to be obtained from the study.

- **Refinement**

Refinement of animal sourcing, animal care practices and experimental procedures to minimise or remove physical and psychological distress, within the limitations imposed by the requirements of the research.

Researchers should guard against any tendency to under-rate or ignore the potential discomfort or suffering of animal subjects, and may not try to achieve cost savings by compromising the quality of care afforded to them.

6.1.2.5 The Ethical Review Process

Every experiment in which sentient animals are used for research, testing or educational purposes must first undergo a formal process of ethical review by the appropriate Ethics Committee.

6.1.3 Other important guidelines regarding the use of animals in research

All relevant South African legislation[51] and the National Code for the Handling and Use of Animals in Research Education, Diagnosis and Testing of Drugs and Related Substances in South Africa and applicable international treaties such as the Convention on International Trade in Endangered Species (CITES) must be adhered to.

[51] The Animal Protection Act 71 of 1962, The Animal Diseases Act 35 of 1984, The National Parks Act 57 of 1976, The Nature Conservation Ordinances of the former four provinces (Cape Province ordinance 19 of 1974, Orange Free State ordinance 8 of 1969, Natal Ordinance 15 of 1974 and Transvaal Ordinance 12 of 1983).

7. RISK ASSESSMENT AND RISK MANAGEMENT

Biotechnology products and other biotechnology activities must be fully assessed for adverse impacts on human or animal safety or the environment. Long-term as well as short-term impacts, including impacts that may not be immediately apparent must be addressed. Risk assessments must be conducted in accordance with accepted scientific principles. Any identified risks must be acknowledged through open and accountable processes.

Where biotechnology applications are developed, risk management strategies must be established to ensure that any risks are effectively managed. Any risk or adverse consequence associated with research or product development must be reported to the relevant authority responsible for product oversight, regulation, risk assessment or risk management. If, after product approval, risks or adverse consequences associated with the product, and not previously apparent at the time of approval, become known, the relevant authority must be informed as soon as possible.

7. WASTE DISPOSAL

Any waste associated with biotechnology activities must be managed and disposed of in such a manner that there is no negative impact on the environment and human health.

In the management of waste, researchers and research institutions, have a duty to comply and familiarise themselves with all national, provincial and local authority legislation dealing with the disposal of waste in his or her possession or under his or her control. As biotechnology activities may involve the work with, or production of substances or organisms which may be hazardous or potentially hazardous to the environment or human health, researchers and research facilities must comply with the provisions of the Hazardous Substances Act[52] where this act is applicable.

In respect of health care waste, the Health Professions Council of South Africa has issued comprehensive guidelines entitled 'Guidelines for the Management of Healthcare Waste'[53]. Health care waste is defined as:

> [H]azardous waste which refers to any material or substance that, if handled improperly, has the potential to harm people, property or the environment. In this regard, all human and anatomical waste, blood and body fluids are considered to be potentially hazardous. The unsafe disposal of such waste could have detrimental effects for people who might come into contact with health care waste.[54]

For guidance in relation to the disposal of health care waste, reference must be made to the Health Professions Council's Guidelines mentioned above which are available at www.hpsca.co.za.

[52] Act 15 of 1973.
[53] Guidelines for Good Practice in Medicine, Dentistry and the Medical Sciences, Booklet 6, issued October 2002.
[54] In terms of the Code of Practice of the South African Bureau of Standards on the Handling and Disposal of Waste Materials within Health Care Facilities (SABS 0248:1993).

8. BIOLOGICAL WEAPONS

Biotechnology must not be used to develop biological weapons for use in human warfare or terrorism, and no assistance may be given to any other organisations, persons or countries to develop, produce, duplicate, stockpile or utilise such weapons. In this regard the Biological and Toxin Weapons Convention of 1972 which South Africa signed on 10 April 1972 and ratified on 3 November 1975 is affirmed.

9. INTELLECTUAL PROPERTY AND COMMERCIALISATION

The provisions of the Patents Act[55] and the National Environmental Management: Biodiversity Act[56], with regard to benefit sharing with indigenous communities, must be respected and adhered to in all instances where application for registration of a patent is made.

Biopiracy may not be practiced in any form. "Biopiracy" refers to the appropriation of developments or discoveries in the area of biological resources, by another party without consent. In this context, discoveries by indigenous communities must be respected and appropriately acknowledged.

When application is made for a patent, the following must be observed:[57]

- The applicant must disclose the origin of genetic or biological resource or knowledge used in the invention in the application, and non-disclosure or wrongful non-disclosure of prior knowledge, traditional knowledge oral or otherwise is unethical (and may have legal consequences in that the application is refused or the patent revoked);
- The informed consent of the owners or holders of traditional knowledge must be obtained, prior to applying for the right to obtain patent protection for any element of indigenous knowledge or heritage, for the sharing of ownership, control, use and benefits. Such consent must be adequately documented and submitted with the application to the Registrar of Patents.

New discoveries by South African researchers must be developed in ways that provide appropriate returns to the State and as far as practical, control must be maintained over the intellectual property within South Africa. Where, despite best endeavours, it is not possible to develop such discoveries within South Africa, the aim should be to license rather than sell the intellectual property.

It must be recognised that other developing countries are also seeking to improve their biotechnology capacity and the exchange of technology between countries must be supported for broader global social development and benefit of the world economy.

Not all biotechnology research may attract significant commercial interest. Research may be pure or strategic, or may be undertaken solely for community service or public benefit reasons. This type of research has much value and importance and is encouraged. A duty exists to pursue research and development which may benefit the South African population, especially the poor and disadvantaged communities, even where such research does not result in commercial returns to the organisation or to the state.

The transactional costs associated with intellectual property should not obstruct access by the poor and disadvantaged populations to new biotechnology discoveries that may benefit them.

[55] Act 57 of 1978.
[56] Act 107 of 1998.
[57] These ethical principles are based on the proposed amendments to the Patents Act.

10. INTERNATIONAL OBLIGATIONS

Any conduct which may violate South Africa's obligations as a good International citizen must be avoided. All relevant laws and standards applicable to other countries in which South Africa conducts biotechnology activities, or to which South Africa exports biotechnology research or products, must be observed.

11. FACILITATION OF DISCUSSION ABOUT ETHICAL ISSUES

Consideration and discussion of ethical issues associated with the specific biotechnology research projects, undertaken by organisations or individual research projects, must be encouraged within research organisations.

Where possible, having regard to the organisation's size and resources, the involvement of qualified ethics advisors to assist in addressing ethical issues and concerns must be considered and implemented where possible.

The rights of all persons to contribute to public debate and discussion about the ethical challenges created by biotechnology must be upheld. Many ethical issues cannot be resolved purely by the organisation or relevant profession engaged in the research and consequently broader perspectives need to be engaged. These broader perspectives must be included in any consideration of ethical challenges.

12. MEDICAL RESEARCH AND HEALTH CARE

13.1 Review by Research Ethics Committees

Research involving humans must be conducted with the highest standards of safety, integrity and respect for human dignity, and must comply with all relevant South African Ethical Guidelines, in particular the Department of Health Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, 2000.

The National Health Act[58] provides for research involving humans and requires that such research must be reviewed and approved by the appropriate accredited Research Ethics Committee established by the institution or in terms of any applicable legislation for the purpose of providing ethical oversight of research proposals and ensuring that research is conducted ethically.

13.2 Human Genetic Research

Genetic research improves our understanding of how human genes and environmental factors interact with each other to impact on our individual health and the health of the population. In addition to the usual ethical concerns that govern research involving humans, supplementary ethical issues exist which are unique to genetic research. These issues arise from the nature of genes and genetic information which, although personal to the actual participant, are shared with family members and unrelated members of the population. The potential for harm to participants, through the use of genetic information discovered during research, includes stigmatisation and the potential for discrimination by, for example, insurance companies and current or potential employers. Subsequently it is important that care be taken to ensure that participants in genetic research are not at risk, due to their participation in genetic research, of being denied the benefits available to other members of the community.

The principle set out in the *Universal Declaration on the Human Genome and Human Rights* (1997) that "everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics and that dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity," must be observed.

Genetic research which involves children requires special ethical responsibilities and protection.[59] Knowledge gained through genetic studies may place children at risk of stigmatization within and beyond the family.[60] It is therefore recommended that genetic research involving children should not be carried out unless an effective intervention is available.[61] In all instances, the information to be gained must outweigh the risk of harm.[62] [63]

---

[58] Section 73.
[59] Medical Research Council of Canada *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* available at www.ncehr-cnerh.org/english/code_2/ (site last visited on 11/02/2005).
[60] Ibid.
[61] Ibid.
[62] Ibid.
[63] The testing of a child for an early onset condition such as polyposis coli, may be appropriate since the knowledge of this disease will affect the treatment options of the child. It would however be inappropriate to test a child for an adult onset disease such as Huntington Disease for which there are at present no effective prevention.

13.2.1 Informed consent and genetic research

Refer to chapter 2.6.4 of this guideline where the basic principles of informed consent are discussed. However, in genetic research, there are additional requirements for informed consent which are discussed in this chapter.

When obtaining consent from the research participant for collection of genetic material and information, the following must be disclosed to the participant to enable him/her to make an informed decision:

(a) The participant is free to refuse consent to participation and s/he does not have to furnish any reasons for such refusal;
(b) Arrangements and protocols will be put in place to protect the privacy and confidentiality of the participant's genetic information with regard to persons who are family members, and individuals who are not family members of the participant;
(c) The manner in which the genetic material and information collected will be used – whether it will be in an identified, potentially identifiable or de-identified form. In the case where the information will be used in a de-identified form, the participant must be informed that it will not be possible to provide him/her with personal research results;
(d) The reliability of the research result i.e. the typical rate of false positives and false negatives and the probability of the development of a serious genetic disease;
(e) That full information of the disorders which may come to light during the research, including the ways in which the disorders are transmitted[64], the seriousness, how variable it is in its effects, and what therapeutic options are available, will be disclosed;
(f) Whether the research may reveal information which could be potentially important to the participant's offspring, family members or another identified or potentially identifiable research participant;
(g) Whether researchers will endeavour to provide information regarding the research outcome. It is important that the participant be made aware if researchers are not intending to provide feedback;
(h) Where feedback will be provided, the participant may choose whether s/he wants to be informed of the results which have an impact on him/her as an individual. S/he must be informed that should s/he choose to know the results, which could include knowledge of a predisposition to a genetic disorder, s/he has a duty to relay this genetic information to the insurance carrier to which s/he belongs and also in any future application for insurance cover.
(i) The participant must know that counseling is available to help him/her understand the implications of receiving the feedback. If the participant does not want to be notified of research results, their decision must be respected;
(j) Should the participant choose to be informed of the genetic research results which impacts on him/her as an individual, s/he must know the following:
    a. That s/he must disclose such genetic information to any third parties that have a legal or contractual right to receive such information i.e. insurance companies. The researcher must

[64] Whether it is dominant, recessive and sex-linked mechanisms and the significance of carrier status.

stress the fact that the participant, if informed of genetic research results which may impact on his or her health, must disclose this new information to the insurance company to which s/he presently belongs;

b. In addition, the participant must know that s/he has a duty to disclose the results of genetic research, where the results may have an impact on the participant's future health, in any subsequent application for insurance.

(k) Should the research generate information about the research participant which may be relevant to the health of family members, no disclosure to family will be made without the participant's consent unless required by rule of law;

(l) Whether information about the participant's family members may be required during the course of the research;

(m) Where researchers may want to approach relatives of the participant, the prior consent of the participant will be obtained. Furthermore, researchers must, when deciding whether or not to recruit relatives, consider the privacy and any sensitivities of the relatives of which they have been made aware, the ways of communication within the family and the balance of potential benefits and harms which may result from their participation in the research;

(n) Whether the research could potentially detect non-paternity or non-maternity;

(o) That the genetic material and information obtained from the research may have uses unrelated to the present research. However, it must be made clear that no material and information will be used unless the prior consent of the participant is obtained for such further use;

(p) Whether the researcher/s have any intention to store the genetic material and information of the participant for future research. Furthermore, participants must know that they should receive counseling with regard to the possible consequences of the future use of their genetic material. If consent for unspecified future use is given by the participant the duration of storage must be disclosed to the participant. Where the participant refuses to future use, his/her genetic material and information must be disposed of at the end of the current research, once the sample storage and record keeping requirements of good practice have been met by researchers;

(q) Should the participants be sensitive to the manner in which their genetic material is disposed of after completion of the research, these sensitivities should be established and recorded at the outset of the research and observed at the time of disposal;

(r) Participants must know that they are free to terminate their participation at any stage of the research. Participants may decide whether or not their genetic material or information may be disposed of where the samples can be identified. The wishes of participants must be respected;

(s) Participants must be informed that disposal on request will not be possible where their stored samples are de-identified;

(t) Occasionally during genetic research, completely unanticipated and unexpected genetic information may be discovered which directly impacts on the participant and his or her family. Where this occurs, genetic counseling is mandatory. However, the participant is still

entitled to make the decision whether or not s/he wants to know the information;

(u) Participants must be informed that genetic counselors will be made available to them throughout the research process and that participants may consult them on a confidential basis at any stage.

The interests of patients who are unable to give proper informed consent (such as minors or the mentally ill) and who require special safeguards must be protected throughout the entire research process.

Refer to chapter 2.6.4.4.1 and 2 where informed consent in relation to persons who are unable to give proper informed consent is discussed.

13.2.2 Genetic Research and Confidentiality

Researchers must ensure that they comply with the basic principles regarding privacy and confidentiality in research, as discussed in chapter 2.6.5 of this guideline. However, the nature of genetic research raises additional ethical issues in relation to privacy and confidentiality which are discussed in this chapter.

The results of human genetic research that become available must be kept confidential by the researcher. The genetic research protocol must ensure effective arrangements for the preservation of confidentiality in relation to genetic information, genetic material and any information derived from studying the genetic material. The preferred methods of storage for protection of privacy of participants are potentially identifiable or de-identified storage methods, which have been discussed in chapter 2.6.5.

Any information the participant shares about his/her family members must be treated as confidential. Individuals should be fully informed of the results of the genetic research and in particular what the implications of the results would be for the family. When genetic research reveals information that may have serious implications for relatives, it should be explained to the participant why the information should be communicated to other family members. It is recommended that in such an instance researchers should seek to persuade individuals, if persuasion is necessary, to allow the disclosure of relevant genetic information to other family members. The researcher should also seek to ensure that treatment, counseling and support are made available to those family members who receive the unsought information.

Where the researchers are unable to persuade the research participant to consent to disclosure of the relevant genetic information to family members who may be affected by this information, the law and ethics[65] provide for exceptional circumstances where confidentiality may be breached. In such exceptional circumstances, the individual's desire for confidentiality may be overridden. The deciding issue regarding whether or not to breach confidentiality is the following: Should the interests of the third party, in terms of the prevention of harms, take precedence over the interests of the individual participant concerned?

[65] Specifically the principle of beneficence.

EXAMPLE:

Where a research participant was diagnosed with a serious genetic disorder or with a predisposition thereto, it would be in the interests of other family members for the researcher to breach confidentiality, if the family could benefit effectively from immediate medical treatment or preventative measures. The knowledge of a serious genetic disorder, or a predisposition thereto, could provide the family member with the opportunity to take preventative actions such as dietary improvements, therapy, surgery or diagnostic measures. Since preventative measure may be effective in averting the manifestation of the genetic disorder, it may be vital and indeed ethically correct in terms of the principle of beneficence, to inform the relevant family member.

Each individual case should be treated on its own merits when making the decision whether or not to breach confidentiality and inform the interested family members. The following principle should be observed in coming to a decision:

- Access by third parties to the personal genetic information of a research participant should be granted only when, on balance, the interests of the third party (family members), in terms of prevention of harms, outweighs the participant's right to privacy and confidentiality.[66] [67]
- The risk posed to the third party must be a real and serious risk and there must be no other means of preventing the harm from occurring, save breaching the confidentiality of the participant.[68]

13.2.3 Genetic Counseling in the context of research

Only health professionals who have appropriate training, skills and expertise may provide counseling to research participants about the implications of genetic research results and any other issues related to such research and results.

Genetic counseling must be made available to participants throughout the research process and all counseling sessions are confidential.

---

[66] In terms of section 36 of the Constitution, any right in the Bill of Rights, which includes the right to privacy, may be limited in certain circumstances. In the context of genetic research, this would involve a 'balancing' between the right to privacy of medical information and the interests of a third party in preventing harm to such third party e.g. family members who may have an interest in knowing the genetic status of a close family member.
Factors that will be taken into account to determine whether or not limitation of any right in the Constitution (in this context the right to privacy) is justifiable are set out in section 36 (a) – (e) as follows:
the nature of the right;
the importance and the purpose of the limitation;
the nature and extent of the limitation;
the relation between the limitation and its purpose; and
less restrictive means to achieve the purpose.

[67] The NHMRC of the Commonwealth of Australia, in their document entitled 'Guidelines under Section 95 of the Privacy Act 1988' at 7, also take the view that the right to privacy is not an absolute right. They state that in some circumstances, the right to privacy must be weighed against the equally justified rights of others and against matters that benefit society as a whole.

[68] British Medical Journal 'Results of Genetic Testing: When Confidentiality Conflicts with a Duty to Warn Relatives' available at www.bmj.bmjjournals.com (site last visited on 21/06/2005).

13.2.4 Genetic research and Insurance

Policy holders have an ethical and contractual duty to disclose any information relevant to his/her health risks and any changes or new information which impacts on their health status to their insurance carrier as soon as such information becomes known to them. Failure to do so would amount to non-disclosure and breach of contract and the insurance company could legitimately refuse to pay the insurance benefits to such policy holder.

In the context of genetic information and applications for insurance cover, one can distinguish three situations:

- Where a patient has previously undergone genetic testing or screening, the predisposition to a genetic disorder is discovered and the results conveyed to the participant. The patient then applies for insurance. In these circumstances, the patient clearly has a duty to disclose such information to the insurance company.
- The patient has a genetic disorder of which he is aware and the symptoms are already apparent and present when application for insurance is made. The patient has a duty to disclose such information to the insurance company.
- A predisposition to a certain genetic disorder becomes apparent through a participant's involvement during medical research.

The third scenario would be relevant in the context of biotechnology research.[69] The participant has a legal duty to disclose this information to the insurance company, irrespective of the fact that it was obtained during participation in research and s/he must be informed of this during the informed consent process.[70] The participant must know that if s/he fails to disclose such information, the insurance company may legitimately refuse to honour the policy. The researcher has no duty to inform the insurance company of the genetic information since the contract is binding between the insurance company and the participant only.

The Nuffield Council on Bioethics states the following with regard to genetic results which indicate the predisposition to develop a certain genetic disease:

> [A] genetic predisposition to disease is not always an indication of future ill health. The probability that a disease will develop can vary greatly. It may also be very difficult to predict for any given individual the age at which a disease is likely to become manifest. Any prediction is further complicated by the fact that environmental factors often play a major role in many late-onset diseases. Thus, in some cases, it will be particularly difficult, if not impossible, for insurance companies to calculate the chance of an individual developing a disease… Huntington's disease, for example, lies at the extreme end of a spectrum. It is a dominantly inherited disease where there is a high level of probability that those having the defective gene will develop the disease. On the other hand, infamilial hypercholesterolaemia

[69] Refer to chapter 16.4.1 where informed consent and genetic research is discussed.

[70] Should the participant choose to be informed whether or not s/he is predisposed to developing a genetic disorder, s/he, once aware of such medical status, must disclose such predisposition in any future insurance application.

> another dominantly inherited disease by no means all of those with a gene will develop coronary heart disease at an early stage and environmental factors such as diet, smoking and exercise may play a major part.[71]

It is recommended that South African Insurance Companies should adhere to their current policy of not requiring any genetic tests as a prerequisite of obtaining insurance because the following dangers are recognised:

- The difficulty of assessing what may be slender evidence on the genetic susceptibility of individuals to develop polygenic and multifactorial diseases (e.g. some cancers and some heart diseases);
- An awareness that ordinary commercial practice will lead companies to be overcautious in their assessment of the risks derived from medical data; and
- The potential for abuse i.e. discrimination.

13.2.5 Genetic Research and employment

Where during genetic research, genetic screening of employees for occupational risks is contemplated, it may only be done in the following circumstances:

- Where there is strong evidence of a clear connection between the working environment and the development of the condition for which genetic screening can be conducted;
- Where the condition in question is one which seriously endangers the health of the employee or is one in which an affected employee is likely to present a serious danger to third parties;
- Where the condition is one for which the dangers cannot be eliminated or significantly reduced by reasonable measures taken by the employer to modify or respond to the environmental risks.

Although it may be appropriate to introduce a genetic screening programme on these limited grounds, it should be done only if accompanied by safeguards for the employee, and after consultation with the appropriate Institutional Ethics Committee.

It is important that when obtaining informed consent from a research participant for genetic screening, it must be disclosed to the participant that if, during the screening process, it is discovered that the participant has a condition which may endanger third parties in the workplace, the researcher may have a duty to disclose this condition to the employer, should the participant refuse to do so.

13.3 Gene Therapy Research

Gene therapy involves the modification of the genetic material of living cells.[72] The practice of gene therapy relates to two groups of cells – somatic cells and germ-line cells. A germ-line cell is a cell which, during the first few weeks after conception, is set aside in the embryonic sex organs to provide, possibly decades later, ova or sperm.[73] A somatic cell is any body cell except a germ-line cell.

---

[71] Nuffield Council on Bioethics 'Genetic Screening: Ethical Issues' (1993) 66.

[72] U.S. Department of Health and Human Services Center for Biologics Evaluation and Research – Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (March 1998).

[73] Germ-line cells may also be defined as the specialised cells that come together during fertilisation (conception) in organisms that reproduce sexually.

The genes carried by each of these two kinds of cells have distinct roles and the distinction is very important. Genes carried by germ-line cells may be transmitted to offspring and successive generations. Genes which are carried by somatic cells have their role in the corporate life of those cells within the tissues and organs of the individual whom they endow.

All research in relation to gene therapy must be directed to alleviating diseases in the individual patients and no attempts should be made through the use of gene modification, to change human traits not associated with disease.

13.3.1 Somatic Cell gene therapy research

Somatic cell gene therapy is similar to current routine therapies. It is seen as a form of medical treatment and is not subject to the ethical principles governing research. Somatic cell gene therapy is allowed under the National Health Act and therefore, by inference, research into somatic cell gene therapy is permissible.

All research into somatic cell gene therapy must comply with the stringent ethical guidelines applicable to human genetic research.

13.3.2 Germ line gene therapy research

Germ line gene therapy involves the insertion of genes into eggs already fertilized or very early embryos. The inserted genes would be transferred to subsequent generations as it has the effect of modifying the human germ line. Research relating to germ line gene therapy is therefore not acceptable.

13.4 Reproductive Biotechnology Research

The highest regard to the dignity, equality and rights of all persons must be had in the application of research and treatment into assisted reproductive technology.

While bio-medicine may offer increasing ability to diagnose, prevent and treat disabilities and birth abnormalities, the fullest respect and support must be given to those with disabilities, those with disabilities who cannot be cured or remedied by biotechnology and those who decline genetic treatment options for ethical reasons.

Reproductive procedures that attempt to fuse human cells with those of animals or other species may not be undertaken.

13.4.1 Genetic Screening and reproductive biology

While pre-natal diagnosis and genetic screening (including pre-implantation screening in the case of in vitro fertilisation) offer expanding tools for assessing and addressing potential genetic disease and birth abnormalities, such technologies may not be employed for non-medical reasons. For example, such technologies may not be employed in order to assist couples wishing to have a child with particular characteristics (such as particular gender, hair colour, intelligence, or physical strength) if these characteristics have no significant bearing on the health of the child.

13.5 Human cloning research

13.5.1 Introduction

Stem Cells

Stem cells are tissue precursor cells that have the ability to self-renew and differentiate into more specific adult cells which are required in the human body.[74] Because of their unique capacities stem cells can be made to grow into different types of tissue, for example blood, nerve cells, organs or heart muscle.[75] Stem cells are found in most tissues and at all stages of development.[76] There are three types of stem cells namely totipotent, pluripotent and multipotent.

Totipotent cells can develop into complete human beings. They are found in the embryo in up to the 16 cell stage and are genetically identical.[77] At present, research involving totipotent stem cells is strictly prohibited.

The early human embryo (5-6 day-old blastocyst) consists of an outer cell layer which develops into the placenta, and an inner cell mass, consisting of approximately 200 pluripotent cells which develop into the fetus.[78] This inner cell mass is the source of embryonic stem cells.[79] Research on embryonic stem cells is allowed up to 14 days of development of the zygote.[80] This may only be done with the permission of the Minister of Health.[81]

Somatic stem cells (adult stem cells) are more committed or multipotent. Their differentiation is limited to one or a few tissue lineages.[82] Despite the ability of somatic cells to differentiate indefinitely, self-renewal is especially low in mature organs and in general their frequency and versatility decline with differentiation.[83]

---

[74] A Dhai, J Moodley, D J McQuoid-Mason & C Rodeck 'Ethical and Legal Controversies in Cloning for Biomedical Research – A South African Perspective' (2004) *SAMJ* Vol 94 No 11, 906.

Potential sources of embryonic stem cells are:

- Fetal tissue that becomes available after an abortion;
- Excess embryos from assisted reproductive technologies;
- Embryos created through in vitro fertilisation (IVF) specifically for research purposes;
- Embryos created asexually as a result of the transfer of a human somatic cell nucleus to a denucleated ovum.

Other sources of stem cells are:

- Umbilical cord blood;
- Fetal blood and fetal tissue;
- Bone marrow;
- Blood;
- Liver; and
- Brain.

[75] Ibid.
[76] Ibid.
[77] Ibid.
[78] A Dhai, J Moodley, D J McQuoid-Mason & C Rodeck 'Ethical and Legal Controversies in Cloning for Biomedical Research – A South African Perspective' (2004) *SAMJ* Vol 94 No 11, 906.
[79] Ibid.
[80] The National Health Act 61 of 2003, section 57.
[81] Ibid.
[82] A Dhai, J Moodley, D J McQuoid-Mason & C Rodeck 'Ethical and Legal Controversies in Cloning for Biomedical Research – A South African Perspective' (November 2004) Vol 94 No 11 *SAMJ* 907.
[83] Ibid.

The use of stem cells is controversial mainly because much of the current research is focused on deriving these cells from human embryos and cadaveric fetal tissue.

Since the use of embryos is one of the main controversies in stem cell research, the embryo must be treated with respect since it is genetically unique and a potential human life.

Cloning

The term 'clone', in its strictest sense, means a precise genetic copy of a life form.[84] At a molecular level, cloning involves the copying of DNA fragments containing genes and amplifying these in a host cell.[85] Cellular cloning involves the copying of somatic cells and growing them in culture.[86] The utility of these types of cloning would be for the testing and production of new medical products.

Reproductive Cloning

The National Health Act defines reproductive cloning as 'the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose'.[87] Research into the cloning of entire human beings, is not ethically or legally permissible and is prohibited by the National Health Act.[88]

Therapeutic Cloning

Therapeutic Cloning involves the process of somatic cell nuclear transfer where the nucleus from an adult cell is injected into a human ovum of which the nucleus has been removed. The National Health Act defines therapeutic cloning as the 'manipulation of genetic material from adult, zygotic or embryonic cells in order to alter, for therapeutic purposes, the function of cells or tissues'.[89]

Where allowed by the National Health Act, research may continue into cloning of genes and cells for specific medical purposes, where such research has been approved by the Minister of Health and the relevant Health Research Ethics Committee.

13.5.2 Prohibited and unethical practices in relation to cloning

In addition to the principles discussed above, the following practices are not allowed and clinicians and researchers must not engage in any of the following: [90]

---

[84] Medical Research Council of South Africa Guidelines: *Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research* (Book 2) paragraph 3.4.2

[85] A Dhai, J Moodley, D J McQuoid-Mason & C Rodeck 'Ethical and Legal Controversies in Cloning for Biomedical Research – A South African Perspective' (November 2004) Vol 94 No 11 *SAMJ* 907.

[86] Ibid.

[87] Section 57 (6) (a).

[88] Section 57 (1).

[89] Section 57 (6) (b).

[90] These ethical principles were extracted from the following sources:
Commonwealth of Australia NHMRC *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research* (1999) 10; Prohibition of Human Cloning Act 2002 No. 144, 2002; Medical Research Council of South Africa *Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research* Book 2 paragraph 3.4.3.2; The National Health Act 61 of 2003.

- Research on embryonic stem cells exceeding 14 days of the development of the embryo;[91]
- The manipulation of any genetic material, including genetic material of human gametes, zygotes or embryos for the purpose of the reproductive cloning of a human being;[92]
- Any activity, including nuclear transfer or embryo splitting for the purpose of reproductive cloning of a human being;[93]
- Import or export of human zygotes or embryos without the prior written approval of the Minister of Health;[94]
- Placing a cloned human embryo into the body of a human or animal;
- Creating or developing a human embryo which contains the genetic material of more than two persons;
- The intentional alteration of the genome of a human cell in a manner that makes the alteration heritable by descendants of the human whose cell was altered;
- Collecting a viable human embryo from the body of a woman;
- Creating a chimeric or hybrid embryo;
- Placing an animal embryo into the body of a human for any period of gestation;
- Placing a cloned human embryo into the body of a woman;
- Commercial trading in eggs, sperm or embryos of humans; and
- Research involving totipotent stem cells.

13.5.3 Surplus embryos derived from IVF treatment

When creating embryos for IVF treatment, in order to respect the potential life of an embryo, clinicians should take care to limit the number of embryos created to those that will likely be needed by the patient during the course of treatment. In so doing, the unnecessary creation of surplus embryos will be limited and the potential for abuse[95] minimised. Ways of achieving this are to:

- minimise ovarian stimulation;
- limit the number of ova fertilized and embryos stored; and
- not start new treatment cycles for patients when clinically suitable embryos are in storage.

Prior to initiating IVF treatment, the written, voluntary and informed consent of the IVF patient must be obtained, as required by law,[96] concerning the ulitisation of excess embryos. All relevant information regarding the proposed use of such embryos must be disclosed to the patient, so that the patient can make a proper informed judgement as to whether or not she would allow the embryos to be used for such research.

[91] The National Health Act 61 of 2003, section 57 – Research on embryonic stem cells may only be conducted up to the 14 day stage with the consent of the Minister.
[92] The National Health Act 61 of 2003, section 57 (1) (a).
[93] Ibid, section 57 (1) (b).
[94] Ibid, section 57 (3).
[95] It would be ethically unacceptable to purposely create 'extra' embryos during IVF treatment solely to have 'spares' for research purposes.
[96] Section 57 (4) of the National Health Act requires consent from the donor of zygotes before such zygotes may be used for research.

Information must be disclosed to the patient in a way that facilitates understanding and research many not proceed unless it is certain that the patient fully understands the implications and consequences of her consent.

Explicit consent for all permissible purposes must be obtained on all occasions from both the mother and father who must be legally competent to give consent. However, the consent of the father is not necessary where:[97]

- The father's identity cannot reasonably be ascertained;
- The father's whereabouts are unknown and cannot reasonably be ascertained; or
- The father is not reasonably available.

Where a dispute arises regarding consent to use of surplus embryos in research, or where the mother or father[98] dies without leaving clear instructions with regard to the use of such surplus embryos, the embryos may not be used in research.[99]

13.5.4 Use of Cadaveric fetal tissue

Cadaveric fetal tissue may be useful as a source of stem cells in medical biotechnology research. Fetal cells are capable of proliferating faster and more often than fully developed adult stem cells. Their usefulness lies in the fact that they are able to rapidly reverse the lost function of the host.[100]

The use of cadaveric fetal tissue in research is a sensitive issue. Clinicians and researchers must treat the fetus and the parents of the deceased fetus with the utmost respect and consideration. The use of human fetal tissue is in itself not objectionable.[101] Although fetal tissue has distinct biological properties, it raises the same ethical issues as raised by the use of tissue obtained from a deceased adult or child.[102] Care must be taken to ensure that women do not seek abortions with an altruistic view to provide fetal tissue for therapy.

The informed consent of both the father and mother of the fetus must be obtained prior to utilising cadaveric fetal tissue. The consent of the father need not be obtained where:[103]

- The father's identity cannot reasonably be ascertained;
- The father's whereabouts are unknown and cannot reasonably be ascertained;
- The father is not reasonably available; or
- The pregnancy resulted from rape.

---

[97] Department of Health *Ethics in Health Research: Principles, Structures and Processes'* 25
[98] Subject to the exception set out in (a) – (c) above.
[99] Commonwealth of Australia NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) 52.
[100] P Schrock 'Fetal Tissue Transplantation' (1997) available at www.hsc.missouri.edu (site last visited on 23/06.2005).
[101] Ibid
[102] Ibid.
[103] Department of Health *Ethics in Health Research: Principles, Structures and Processes'* 25

In obtaining informed consent from the parent/s for the use of the cadaveric fetal tissue it must be disclosed that:[104]

- The fetal tissue is to be used in research;
- The research is not intended to provide medical benefit to the donor of the tissue;
- The research is voluntary and the patient may refuse without having to give any reasons why. In addition, refusal will not in any way affect the quality of clinical care;
- Whether or not the results of the research could have commercial interest;
- The donor will receive no financial or other benefits for the donation or from the research or from any commercial products;
- Where the research will derive cell lines, whether or not the information could be used to identify the tissue donor, or whether the identifiers will be removed prior to the use or derivation of the cell lines;
- Where the fetal tissue or derived cell lines may be used in clinical transplantation, that such research will be carried out altruistically and the donor may not direct into whom the tissue or cell lines will be transplanted;
- Where the tissue or derived cell lines will be used in clinical transplantation, whether the identity of the donor will be disclosed to the recipient;
- Derived cell lines or cell lines may be stored for many years and shared with multiple researchers at various research institutions.

13.5.5 Payment for donated tissue, embryos and fetal tissue

Payment for any human tissue is unethical and unlawful due to the potential for abuse. In terms of the National Health Act[105] it is an offence for a person who has donated tissue, a gamete, blood or a blood product to receive any form of financial or other reward for such donation, except for the reimbursement of reasonable costs incurred by him or her.[106] It is also an offence to sell or trade in tissue, gametes, blood or blood products.[107]

[104] Juvenile Diabetes Research Foundation International *Policy Statement/Guidelines for the Use of Human Fetal Tissue in Research* February 2003 available at www.jdrf.org (site last visited on 23/06/2005).
[105] Act 61 of 2003
[106] Ibid Section 60 (4) (a).
[107] Ibid Section 60 (4) (b).

Ethical guidelines for good practice in the health care professions

The following Booklets are separately available:

Booklet 1: ***General ethical guidelines for health care professions***

Booklet 2: ***Ethical and professional rules of the health professions council of South Africa as promulgated in government gazette R717/2006***

Booklet 3: ***National Patients' Rights Charter***

Booklet 4: ***Seeking patients' informed consent: The ethical considerations***

Booklet 5: ***Confidentiality: Protecting and providing information***

Booklet 6: ***Guidelines for the management of patients with HIV infection or AIDS***

Booklet 7: ***Guidelines withholding and withdrawing treatment***

Booklet 8: ***Guidelines on Reproductive Health management***

Booklet 9: ***Guidelines on Patient Records***

Booklet 10: ***Guidelines for the practice of Telemedicine***

Booklet 11: ***Guidelines on over servicing, perverse incentives and related matters***

Booklet 12: ***Guidelines for the management of health care waste***

Booklet 13: ***General ethical guidelines for health researchers***

Booklet 14: ***Ethical Guidelines for Biotechnology Research in South Africa***

Booklet 15: ***Research, development and the use of the chemical, biological and nuclear weapons***

Booklet 16: ***Professional self-development***