"Primum non nocere" ("First do no harm")

Medical ethics standard attributed to Hippocrates. This Oath became obligatory for physicians prior to practicing medicine in the 4th century AD

Everyone agrees there is positive value in ensuring, providing and obtaining Informed Consent when contemplating research with human subjects. For most researchers informed consent is now accepted as an ethical requirement of the research process. (5) Given the atmosphere surrounding medical research in the United States today, no one is willing to publicly renounce the concept. The fireworks begin with the discussions about how to define Informed Consent, who can give and who can get Informed Consent, what information needs to be disclosed in Informed Consent Documents, how much is to much, what constitutes coercion. The major problem is that there is no agreed upon, standardized method to determine adequate informed consent. 56 57 The differences in opinion emerge when we approach Informed consent as a process, not a document. At the center of this debate is the volunteer/subject/ participant or patient. Without this "researchee" there exists no way for the "researcher" to test his theory. It is the welfare of this central, critical element that must be ensured. The culture of individual rights has evolved over the last two centuries. The ancient Greeks, Romans and Egyptians did not practice such a concept. #13 This has brought moral and legal dilemmas that must be discussed and addressed.

Respect for persons requires that they be allowed to choose what shall happen to them to the extent that they are capable of understanding. This year, more than 15 million Americans will be recruited into clinical trials. Some will be healthy, alert adults, some will be very ill fragile children-Volunteers will have many faces. Just as the trials will have differing goals, so will the individuals participating in them. The financial stakes are high. Billions of dollars will be invested in this endeavor and there will be both profits and losses. The many interested parties include government regulatory bodies, academic centers, ethicists, commercial interests and the public at large. The immense challenge is to create a system/process that will adequately respond to all. These are challenging times in clinical research. #1 With too much focus on the patient as a subject, there is the chance that there will not be enough focus on the patient as a human being. #1

Key Question-How can the Informed Consent Process be constructed to obtain the maximum value for all concerned?

Medical research is the key to the development of new treatments, new drugs, new devices, new procedures and life saving changes in medical care for human beings. Clearly, that medical research can not be conducted without volunteers. It seems that this would be fairly simple given the high regard most people have for the medical community in general and physicians in particular. For thousands of years people have attempted to help and heal their fellows. Often, this took a benign course, but close inspection reveals documented examples of horrible exploitation and research that appears to have been more 'experimentation' then true research or care. Formal research, according to Roberta Kalechofsky, PhD. may have found its beginnings in the nineteenth century with the rise of the experimental method in science, and subsequently in medicine. She says," The history of human experimentation in the West is usefully divided into two eras: before the Nazi era and after. Human experimentation neither arose with the Nazis, nor ended with them."

The best known recent examples are surely the awful experiments that were conducted at Buchenwald, Auschwitz and other camps during the fall of 1939 and through the spring of 1945. Despite the existence of the 1900 Berlin Code, #15 that expressly required that the human subject, in research interventions, must have given his "unambiguous consent" and that there must be proper explanations, researchers proceeded as they wished. Well over two hundred medical doctors were involved; yet later, attempts to expose and punish them ran aground when it became clear that the world governments had no defined principles that covered medical "research" and prosecutors were forced to charge the perpetrators with murder and crimes against humanity (footnote this) instead of accusing them of the horrible crimes committed during their 'research'. As a result the famous Nuremberg Code, the first international document to provide research ethics guidelines was developed. An interesting side note is that many American and European medical personnel felt that the code was unnecessary and did not apply to them. This had far reaching consequences in the years to come. The Nuremberg Code made voluntary consent and freedom from coercion necessary conditions of clinical research studies. In addition,

participants must be able to comprehend the risks and benefits of their participation and feel free to leave the project or study if they choose.

What Happened: History

Anthony S. Kessel says that the word ethics refers to the general beliefs, attitudes or standards that guide customary or community behavior. # 10 Ethics and healthcare have been the subjects of debate and discussion for centuries. However, biomedical ethics - synonymous with medical ethics or healthcare ethics - developed as a discipline of its own in the 1960s, initially in the United State. The emergence of the scientific era, with it's bursts of curiosity, eruption of information and the explosion of knowledge brought about radical changes in medicine. But the need to know and the urge to explore and discover reasons vastly predate the 1900's.

Cleopatra is said to have wondered about the time it took for a male fetus to develop. She supervised experiments among her maids to test the theory that male fetus was fully developed in 40 days and a female in 80. Her servants were impregnated and killed at differing times of gestation to find the answer. # 7 Wera Sharav records that the Book of Daniel tells of meat and vegetable experiments that were done using Jewish prisoners.

Dr. Edward Jenner infected a local child with cowpox and three months later with smallpox in 1776. This lead to widespread policies of vaccination and the eventual eradication of smallpox. However, rarely if ever, is this early researcher criticized for his 'use' of the neighborhood child, an expendable person.

In1895, the famous chemist E.E. Slosson wrote (and was published in the New York Independent), "A human life is nothing compared with a new fact in science…" #14

In 1913 the Pennsylvania House of Representative recorded 146 children that had been inoculated with the syphilis virus "through the courtesy of various hospitals" and that others had had tuberculin put in their eyes. Several of these children became blind. The experimenters were not punished! #14

In 1931, Dr. Cornelius Rhoads, under the auspices of the Rockefeller Institute for Medical Investigations, infected human subjects with cancer cells. He went on to establish U.S. Army Biological Warfare facilities and was named to the U.S. Atomic Energy Commission. While there, he began a series of radiation exposure experiments on American soldiers and civilian hospital patients.

Of great concern, is that frequently, these individuals experienced slight, if any, degree of censure at the time of their research and rarely suffered negative consequences. They often *advanced* in their careers, earning professional respect and financial stability. This heritage has lead many to continue to advance the defense first suggested by Celus, a physician in the 1st century AD. He is quoted as saying, "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." #20 This certainly supports the use of the ongoing recruitment and use of expendable, vulnerable and disadvantaged individuals in clinical research.

Even after the Nuremberg Code was written and accepted, many in the United States continued to experiment under their own individual policies. Perhaps this was encouraged by the fact that although the Japanese had conducted experiments very similar to the Nazi's (many on American prisoners of war) during the war, the United States government choose to not pursue punishment in exchange according to the Advisory committee on Human radiation Experiments for the information gleaned during those experiments. # 19 # 14,

Almost all researchers have now heard of the infamous Tuskegee situation, conducted under the auspices of the United States federal government. Those individuals and their families received a belated apology from President William Clinton in 19_____. Even a cursorily look at more recent events shows an ongoing difference in belief systems and personal and institutional practice.

More recent examples collected by the Association for Human Research Protection include:

1940's and 1950's - The Atomic Energy Commission continued to follow studies that involved giving civilian's cereal that had radioactive tracers.
1947 - The CIA began its study of LSD as a potential weapon for use by American intelligence. Human subjects (both civilian and military) were used with and without their knowledge.

1950 – The Department of Defense began plans to detonate nuclear weapons in desert areas and monitor downwind residents for medical problems and mortality rates.
1950 - In an experiment to determine how susceptible an American city would be to biological attack, the U.S. Navy sprayed a cloud of bacteria from ships over San Francisco. Monitoring devices were situated throughout the city in order to test the extent of infection. Many residents become ill with pneumonia-like symptoms.
1956 – The U.S. military releases mosquitoes infected with Yellow Fever over Savannah, Georgia and Avon Park, Florida. Following each test, Army agents posing as public health officials tested victims for effects.
Through the 1960's the CIA experimented with LSD on institutionalized patients and continued until 1970 with members of the military.
1990 - More than 1500 six-month old black and Hispanic babies in Los Angeles were given an "experimental" measles vaccine that had never been licensed for use in the United States. The CDC later admitted that parents were never informed that the vaccine being injected to their children was experimental.
1995 - Dr. Garth Nicolson, uncovered evidence that the biological agents used during the Gulf War had been manufactured in Houston, Texas and Boca Raton, Florida and tested on prisoners in the Texas Department of Corrections.
And the list goes on…..

More recently, both the University of Pennsylvania and Johns Hopkins University experienced terrible human research tragedy when research subjects died as a result of their participation in clinical research. (Truog, MD)

Jeffery Cohen, et al, states in the CITI course on Protection of Human Research Subjects that the development of regulations to protect research subjects was driven by scandal in research and as such" reflects social concerns " about research. #20

According to the Alliance for Human Research Protection, 36 problems that contribute to ongoing misconduct and serious problems in human research include:

- Research is increasingly driven by commercial concerns.
- Conflicts of Interest are ubiquitous.
- Disclosure of risks may be incomplete.
- Regulatory safeguards have been violated.
- Lax oversight by Institutional Review Boards has failed to prevent ethical violations even at major research institutions (e.g., University of Rochester, Duke University, University of Oklahoma, Fred Hutchinson Cancer Center, Harvard University, and the National Institutes of Health).

Ernest Prentice, Ph.D. #16 said in a January 2006 presentation at the University of Michigan that other factors include the realities that large multi-center clinical trials are the norm, more drugs and devices are entering the testing phase, more studies require more subjects and IRB's are becoming chronically overloaded and under-resourced.

The Current Situation

Agard defines Informed consent as "an individual's autonomous authorization for a medical intervention or participation in research." 35 All experts and the federal regulations refer to the informed consent process, thus separating the document from the greater, ongoing process of ensuring the consent of the participant throughout the entire study or trial. The national Cancer Institute refers to the document as the foundation of the informed consent process. 41 The form does not represent the process and the process does not end with the form. 43 The informed consent is a process designed to inform potential participants of the important facts about a clinical trial to help them decide if they with to participate. 42

The questions arise in deciding such issues as who can get and who can give informed consent. This is legally defined in federal and often state laws, but there is major, public debate concerning children and the age and abilities that they must meet to provide proper informed consent. This extends to questions about the elderly and those with mental handicaps. In addition, by virtue of their age and medical problems elderly individuals are likely to face greater risks from any given study and will require extra care on the part of the designers and researchers. This in turn results in higher costs. Those with mental

handicaps are not formally covered as vulnerable populations. (legislation has been proposed, but never passed) These individuals, including those with Alzheimer's are widely perceived to need special protection in the research process, especially in the area of informed consent.

The information that must be included in informed consent documents is clearly provided in the Code of Federal Regulations. (Appendix) In addition a number professional organizations such as the American Psychological Association have written and published their own codes of conduct and guidelines.

Internal Review Boards (IRB's) are charged with preventing payments and other incentives that are coercive. But, how much is too much? Compensation must be proportional to time and risk

Informed consent is increasingly being viewed from a legal point of view. #12 According to Kour, in 1992, Informed consent is "usually taken for granted, poorly understood and inadequately practiced." We have entered a litigious time # 16 as evidenced by Alan C. Milstein involvement in over 10 major lawsuits involving clinical research against major Universities and Medical Centers. This public display and the ensuing debates and defenses have caused a well documented erosion of public trust. #16 It has prompted the national Cancer Institute to include a statement on their website that the Informed consent Document is not a legal protection for the provider, but designed to protect the participant. 40

Questions, Issues and Who Cares:

Different populations have vastly different requirements in their information needs and not all decisions require the same level of information. Levinson (6) has explored decision making among physicians and their patients and concluded that not all patients wish to participate. She advocates that physicians and, by extension, other health care providers need to encourage patients to actively take part. Her position seems to be gaining popularity and blends with other discussions of the appropriateness of the Informed consent process. There is ongoing debate about the amount of information to be included. 35Some advocate the legalistic 'reasonable person' position-what a reasonable person in similar circumstances would want to know. This is applicable for medical decision making, where a patient finds themselves in a definable medical situation with predictable risks and outcomes. But the subject/volunteer does not need to be in this situation. Frequently they are healthy volunteers and as such, it might be argued, need a great deal more information to decide if participation is appropriate.

The Players

Patient populations

Women have seen a change in the public attitudes surrounding research since the federal regulations of 1973 strictly prohibited their participation. (a reflection of a more paternalistic and protective view in society) Nineteen ninety three (1993) saw a 180 degree shift with the recognition that women might not respond to medication the same way that men responded and that extrapolation of data from men would not be appropriate. Martha Elks #9 says that strong focus on the protection of patients resulted in other problems, among them a lack of adequate studies among women and minorities, as well as decreased access to new treatments, drugs or therapies. Separate trials needed to be done to uncover differences. In addition, women needed to have trials done that reflected diseases and conditions that occurred in women only. Study trials were now mandated to include women. A new appreciation for the gender differences also resulted in the recognition that race and ethnicity may affect research results and inclusion of other groups was encouraged. A great deal of concern was expressed for pregnant women and their fetuses. This was reflected in changes in study design to ensure that the unborn were not exposed to drugs and that the women involved were aware of the risks. The informed consent document frequently became much longer when these concerns were addressed. Additionally, there is a debate concerning the rights of the pregnant women to expose her unborn child to study medications-resulting in confusion over details in the informed consent documents.

Children are well represented in studies of life-threatening pediatric diseases (including cancer and severe infections) but studies of treatments and medications for less serious conditions are often lacking. #9This, despite incentives that are offered to drug developers in the form of increased patent time and even funding to study drugs that have moved to the generic stage and are no longer profitable to the original developer. Careful design of such studies and efforts to include children are important. Most

people are comfortable with offering a very sick child (or their parents) a chance to receive a potentially lifesaving drug, but it is quite different to contemplate having healthy children take medication in order to determine the correct dose for cough medications or even epilepsy control. The issues of incentives (a critical element of the informed consent process) is being hotly debated, with some researchers declaring that any incentive is inappropriate, some that only expenses should be reimbursed (parking, gas) and others that a savings bond or gift certificate for the child is appropriate. The goal is to avoid having caregivers place children in trials for the cash.

Veterans come under special protection of the federal government and the Veterans health system has a separate system governing research done in their facilities. This is especially stringent in studies that concern the storage of tissue or blood. Frequently researchers who want to include veterans in multi-site studies find that they need to develop multiple informed consent documents to meet the different regulatory groups. This can present a problem with ensuring that all participants receive the same information.

Prisoners have been an exploited group for centuries. Prized as research studies since they had few rights, were easy to locate and follow up, they underwent inappropriate studies. Currently, they are in a position that some prisoners view as negative. Federal regulations prohibit any research without extremely stringent controls. No privileges, such as sentence reduction, can be provided as a result of volunteering for research studies. Because compensation can not generally exceed what a prisoner can make in a day (often $1.00) the correct choice of an incentive is difficult. These difficulties and the generally low literacy rate seen in the prison population make ensuring informed consent difficult.

While frequently valuable members for a research study, groups of individuals in crisis present special problems with the informed consent process. The bereaved are undergoing an emotion event and are often unable to utilize their usual level of skill to address choices and plan participation. Similarly, the intensively ill may see clinical trials as treatment, refuse to be in placebo arms or be influence by support groups #2 Patients encountered in the emergency room may be extremely ill, unable to concentrate on choices for a medical event that was unplanned, they may even be unconscious and present problems with who can give consent for emergency research. This problem is encountered in the intensive care units (ICU's) and is blamed for a serious lack of research there (#)

Lastly, mention must be made of the problems encountered by the illiterate in attempting to understand a written document. New research is also focusing on those who are "health illiterate", meaning that they do not understand the terms used by medical personnel to describe health conditions. This extends to those that do not recognize common terms for medical events as well as the formal medical terms or jargon.

Researchers

The need to publish trial results has been criticized as a driving force behind researchers encouraging individuals to participate in studies. 54Some argue that inappropriate use of the informed process has resulted in subjects beginning trials that they are not qualified to participant in and that they may not have chosen had they better understood the risks and benefits. Intensive criticism has arisen concerning conflicts of interest, with researchers holding stock in companies that are developing the drug or device. This has lead to an increase in the informed consent document, as additional paragraphs must now specify who will benefit from the trial. Another problem is the ever increasing demands for their time. Some academic centers are reviewing how to reduce clinical responsibilities to allow researchers time to spend on their studies. This time crunch has lead to the delegation of the actual procurement of signatures on the informed consent document. While the Principle Investigator (PI) is ultimately responsible, most do not actually sit down with their patients and review the document and the process. Variability in explaining the study and the informed consent process has been identified as a serious issue.

Health Care Providers

Academic Centers face legal issues as well as status and financial concerns. David Orentlicher says that for some studies, we must worry whether research subjects are placed at too great a risk by physicians seeking to advance medical knowledge. Barclay and/ Kerridge raise issues concerning medical decisions

are made. They question the role that intellectual stimulation, commercial interest and academic self-interest play in the conduct of studies. The concern is always that these interests may over ride good clinical practices and the welfare of the study participant.

Private Practioners

David Orentlicher has pointed out that numerous writers have indicated that financial incentives can lead clinical investigators to persuade patients to enter clinical trials that are not necessarily in the patients' best interests. As more and more studies are proposed, the pool of available subjects needed to be widened and the private practitioner is being targeted for drug studies. He has advanced a highly controversial suggestion that patients be required to take part in research as a requirement of treatment. 54The Washington Post reported on January 25, 2006 that a panel of prestigious panel of medical experts fear that conflict of interest is increasingly becoming a serious issue, possibly influencing doctor's treatment decisions and scientific findings.
Conflicts of interest may bias investigators' presentations of information.

Third Party Interests
Medicare will now pay for certain tests and care, used for research purposes, which ordinarily are being obtained in the course of regular medical. This seemingly positive move is full of pitfalls form an accounting perspective and often researchers are reluctant to utilize this method to cut down expenses for fear of the accusation of fraud.

Drug Developers/Pharmaceutical Companies
The pharmaceutical industry has a multi billion dollar stake in the research carried on in the United States. Criticized for their profits (which actually are below that of the newspaper industry) they point to the soaring costs incurred in developing drugs and the extraordinary financial difference that a few months more of patent time will make. At this time the United States leads the world in the development of new drugs and unfortunately they are also leading in the erosion of public trust. The industry has a great investment in each study they begin and the informed consent process is essential to obtaining accurate results. (i.e. the study participants must qualify appropriately-people must not misrepresent themselves in order to volunteer for studies and obtain cash incentives) They also are encountering many challenges in writing informed consent documents for multi-national trial sites. The culture variations in power and community often affect who must receive information and who can give informed consent.

The Regulations

Over the past half-century, the international and U.S. medical communities have taken numerous steps to protect people who take part in clinical research. The following timeline provides an overview of some of the key events that have contributed to the development of the current system.

The Nuremberg Code 1947

Following the trial of 23 Nazi medical personnel, the Nuremberg code was adopted by the United Nations General Assembly in 1948. This Code was the first major international document to provide guidelines on research ethics. It provides an ethical standard for the conduct of research, defining boundaries for risk, experimentation and investigators qualifications. Among other principles, it formally made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if:

- Participants are able to consent
- They are free from coercion
- They understand the risks and benefits involved.

The Code also states that researchers should minimize risk and harm, making sure that risks do not significantly outweigh potential benefits. They must use appropriate study designs based on animal experiments, and guarantee participants' freedom to withdraw at any time.

Declaration of Helsinki 1964

This sentinel document, regarded as the worlds' most recognized source of ethical guidance on research #18 begins with stating the mission is the safety of the patient. (CHECK wording)The World Medical Association adopted 12 principles to guide physicians on ethical considerations related to biomedical

research. These guidelines were revised at subsequent meetings in 1975 (Tokyo, Japan), 1983 (Venice, Italy), and 1989 (Hong Kong). Agreement with this document must be referenced in any application for federal funding.

The National Research Act 1974
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was charged with identifying the basic ethical principles that should govern medical research involving people. They were to produce and recommend ways to improve the Regulations for the Protection of Human Subjects.

The Belmont Report 1979

The Hippocratic Oath includes “first do no harm”, a concept incorporated into the 1974 Belmont Report under the description of beneficence. This document is considered to be the premier reference for the protection of those who participate in research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." sets forth three principles underlying the ethical conduct of research:

Respect for persons: recognizing the autonomy and dignity of individuals. Everyone must be accepted without regard to their age, race, sex or other factors. There is a need to protect those with diminished autonomy. The report recognizes that some individuals are not able to make their own decisions.

C.Weijer #**8**. says that the principle of respect for persons requires that the wishes of autonomous persons be taken seriously, and those who are not autonomous are protected. The principle finds expression in requirements for informed consent and confidentiality.

Beneficence: an obligation to protect persons from harm by maximizing benefits and minimizing risks. The potential for risk must be justified by the potential for greater good for society. Anthony S. Kessel says that generally there is an assumed beneficent goal in promoting the welfare and health of the patient. In healthcare research the beneficent goal is more complex. It is this additional complexity that must be addressed in questions of conflict of interest. David Orentlicher says clinical trials are critical for screening new drugs and determining their effectiveness. Many individuals enroll in clinical trials in order to get access to new medications not yet available on the open market. On the other hand, participation in a clinical trial is not always necessarily beneficial to the participant.

Justice: fair distribution of the benefits and burdens of research (shared equally among different types of persons, including sufficient numbers of differing populations) This principle is designed to ensure a fair selection of subjects #18

The Belmont Report goes on to explain how these principles apply to research practices. The report also makes it clear that other principles may apply and that at times these principles may be seen to be in conflict with each other. The goal is to provide a framework to guide the resolution of ethical problems in research.

Code of Federal Regulations 45CFR 46

Internal review of human research protocols with respect to the rights, welfare, risks, benefits, and informed consent of the participant was mandated by the Surgeon General in 1966 and extended to apply to research funded by Public Health Service grants. This published code is widely available and is the basis for research conduct in the United States.
Regulations are created and oversight is provided by the FDA and the Office of Human Research Protection (OHRP) FDA regulations pertaining to IRB’s can be found in section 21 of the Code of Federal Regulations part 56. (21CFR56) The OHRP regulations are in 45 CFR 46. In 1991 the IRB and informed consent regulations were revised and are found in the ‘Common Rule. #18 This policy was adopted to ensure a uniform system of protection for those who participate in research conducted or supported by all federal agencies and departments. In 2001 (?) the Department of Homeland Security joined over sixteen other agencies and departments in recognizing and agreeing to adhere to this policy.

Medical Procedure consent and Research consent

Most malpractice suits begin as a result of errors with informed consent according to an ad, for an audio conference on tape, on Healthcare Marketplace, sponsored by Medical Staff Briefing. In an interesting second sentence they point out that clinical trial patients are also filing litigation alleging the lack of informed consent.

There are many similarities, but some striking differences in the use of informed consent documents in general medical care and treatment and the research situation. At times, they may overlap, but as stand alone documents the usual medical form is much shorter and considered a formality by many patients and their caregivers.

Dr. Panduranga Rao, a University of Michigan Nephrologist and researcher, in a personal interview, stressed that he believes that the most vital difference is the concept of risk. During a common medical procedure the risk is well known and quantified. Despite differences in complication rates between medical centers or hospitals, there is general consensus concerning the risks. In addition, the patient often sees the treatment as inevitable, a necessary corollary to his illness or condition. Research on the other hand, is not required of the patient and the level of risk may not be known or widely agreed upon. Common medical procedures are generally clear about the time required for the event and subsequent follow-up. Research studies must specify the time involved, but this is time that is not required for the subjects medical care and is time that could be spend in other pursuits.
Medical institutions have specific requirements that govern which staff members may obtain consent. (written or verbal) State and local laws may also be in effect and influence who may give consent for medical procedures. While the healthcare providers are considered responsible for ensuring the patients understanding and agreement, the institution itself usually must bear the ultimate responsibility for obtaining the signature and the ultimate outcome of the procedure. Research guidelines and good clinical practice (GCP's) are absolutely clear that the Principle Investigator is the one responsible for the conduct of the trial, the informed consent process and any outcomes during the trial or study. 30
Research teams are entering increasingly difficult discussion around the subject of who can ultimately give consent in areas concerning children, pregnant women, the fragile and vulnerable-including those with mental handicaps.

Individuals who embark on medical treatments may be able to stop the treatment or procedure at will. They may, however, encounter medical complications and come under pressures to continue. Individuals in general research trials are guaranteed the right to stop at any time (a critical element when reviewing the patients understanding of the informed consent form). Those in some treatment/research trials may fall into a gray zone. Examples include some device trials (artificial hearts) where the recipient may decide to withdraw from the study, but must continue with the medical care.

An interesting addition to many standard medical consent forms for common medical procedures is the added page that includes permission for the institution to keep/own tissue, blood or other fluids obtained during the procedure for research. These forms give the institution the right to do any type of future research and to use the specimens for purposes that may lead to profitable outcomes. A concern is being raised about these generic statements being tucked in with consent forms that have consistently not been carefully discussed with the patients. These specimens may be subsequently used for gene analysis and expression. Without doubt, these are topics that must be discussed with greater input.

Factors That Influence the Informed Consent Process:

Factors that impact the understanding and comprehension of written documents vary by person and situation. Predictors of understanding include levels of education, attitudes and perceptions, the degree to which the consent is read and the perceived clarity of the information. In addition, the subject's assessments of the risks and benefits (considered a critical area of understanding) was influenced by the amount of information and the environment in which the consent was sought. #22 #30

Culture
Educational and financial status may have a profound impact on a patient's experience of power in the medical setting. #2 Gender differences may impact power dynamics #2. In some cultures and environments, women may be subservient to their husbands, fathers or others.

Studies in the medical setting, on truth telling and disclosure indicate that some patients may come from a cultural or ethnic background that discourages or finds it inappropriate to raise concerns or create anxiety for patients. Factors that interfere with the consent process include hesitation on the part of the volunteers to ask **questions,** variable presentation of the content, and difficulty verifying the volunteers comprehension #1, 2

Education
A satisfactory informed consent process for clinical research can be elusive under the best of circumstances. Prospective enrollees may be limited in their understanding of the process by poor linguistic education. For many potential subjects, language is a significant issue, determined by the culture from which they came, and their ability to understand verbal or written instructions, whether or not they speak English. There are additional issues when English is not the individual's first language. They may be quite adept in ordinary day to day matters, but not be equally conversant in medical terms.

Environmental Issues & Serious Illness
Concerns have been raised about the situations in intensive care units and emergency rooms that severely restrict the time that is available to explain research studies to potential subjects. This issue has generated special consensus conferences #29 to search for ways to adequately address the questions of who can sign informed consent documents, possible waivers of informed consent and how much is the minimum information that should be provided to seriously ill individuals. Questions have been raised about the likelihood of any single individual arriving in the emergency room without adequate identification. The possibility that certain groups of people (homeless, the undocumented) will make up the majority of those who are unable to indicate their preference or have a legal advocate has added to the discussion. In addition, concern has been raised that certain types of research will come to a standstill if more stringent regulations are put in place. # 44

Risk
Factors that influence who will participate include risk levels as well as negative media attention #1 Bogardus and others have focused on three risks that may occur specifically as a result of the unnecessary participation in research. #8 1) Physical risks: the research subject may suffer bodily harm - minor or serious, temporary or permanent, immediate or delayed 2) Psychological risks: study participation may impact upon the research subject's perception of self, cause emotional suffering, e.g. anxiety or shame, or may induce aberrations in thought or behavior and 3) Social risks: research findings, or even study participation itself, may expose subjects to the possibility of insurance or employment discrimination, or other forms of social stigmatization. In addition, there may be economics risks: research subjects may directly or indirectly bear financial costs related to research participation. Jaynes, says the informed consent forms that contain long lists of risks (no matter how unlikely they are to occur) can be as harmful as too little information. 30

Trust
The recent scandals and problems in the clinical research arena have lead to increased scrutiny and regulation by the federal government. 38 While acting director of the OHRP, Bernard Schwetz, D.V.M., PhD. Said "It's important that we have the rapport with the public that allows them to trust us with this program." 39

Health Literacy

It might seem redundant to suggest that written educational materials should be readable by the clients to whom they are given. Twenty percent of Americans are functionally illiterate #11 and ninety million Americans are reported to have low literacy skills. #21 It should be clear that clients with low literacy skills will require special interventions to help them learn. In 2001, Houts et al. suggested that pictographs could be useful a tool. Their series of studies suggest that the addition of pictographs assist individuals with low literacy (less than 5th grade) to retain large amounts of medical information for significant periods of time. #25 In 2005, the concluded that pictures closely linked to written text can "markedly increase attention"…."recall of health education information." They also cite improved comprehension when the pictures show relationships among ideas. 26

Health literacy is #11 a concept that includes both the clients' ability to read the information presented and the ability to comprehend and act on the medical instruction.Many, such as Schillinger (get documentation) believe that low health literacy may have a negative effect on health outcomes and

may be more common among minorities. In 2004 Freda reported a study that found that 80% of women who were eligible for a screening test agreed to have the test, later 38% of them could not describe the test and 72% did not understand the results! Clients are routinely asked to read informed consent forms and then sign them, thus agreeing to undergo tests or procedures they may or may not fully understand. A lack of "health literacy," a concept that denotes not only the clients' ability to read but also to comprehend and act on medical instructions, can influence health outcomes.

Readability & Patient Education

#11 Research over the past twenty years shows that patients rarely comprehend or even recall an adequate amount of the information they have been given. One reason may be that the vast majority of patient education materials are written at readability levels that are far above the average person's ability to comprehend (usually at least four grades higher than average readability) #23 A quarter of Americans are functionally illiterate, with half reading at or below the 8th grade level. 58The average Medicare subject reads at a fifth grade level. 52 The average adult in the United States reads at about the sixth to eighth grade reading level, even if their total number of years of education far exceeds that grade level.45 Robinson et. al makes the point that participants that fail to understand may create their own incorrect interpretations and their consent or refusal to consent may be therefore be based on inadequate information. (45) Horchhauser supports the research that comprehension levels have been shown to be low, but points out that most studies show that lowering the reading level helps only modestly. ACT 4/1/04 46
Many researchers use the Flesch Reading Ease/Flesch-Kincaid Grade level tools. These are easy to use as they are installed on Microsoft Word. Others have advocated for the SMOG test (Simplified Measure of Gobbledygook) 58

Quoting the 1992 Adult Literacy in American Report, Tait says that desired target levels for readability are reading grade levels of 7 to 8 and process ability scores of either 61 to 80 (good) or 81 to 100 (excellent) # 23 45 quotes research that indicates that materials using 6th to 8th grade readability are more effective and have a higher rate of recall. Cardinal recommended that forms be written between the 4th and the 8th grade level. On December 15, 2006, The National Adult Literacy released their latest study. Their results were not dramatically different from the 1992 report. 34 58

Freda makes the point that patient educational materials from the American Academy of Pediatrics, the Centers for Disease Control, from most pharmaceutical companies, from the National Cancer Institute, and from the American College of Obstetricians and Gynecologists have all been analyzed and found to be written at readability levels of grades 10 to 17.

Modified Forms / Simple
Coyne et. al's research in 2003 concluded that consent statements can be modified to be easier to read without omitting critical information. They conducted a study in 44 institutions and found that patients in the intervention (modified form) arm had significantly lower consent state anxiety and higher satisfaction scores. But, they did not demonstrate increased comprehension y use of the modified form.

Interesting results were found by Tait, et all #22 in 2005 after a study comparing modified (grade level 7) and standard (grade level 11.2) informed consent forms given to parents of children considered for research trials. Overall, parent's perceptions of their understanding of the information were high. (This did not match the assessors' measurements of understanding) Parents receiving the modified form did have greater understanding of the trial, but this did not influence their decision to consent. Parents overwhelmingly preferred the modified form (81.2%) but the comments from both groups are important to consider in designing informed consent documents. Those who preferred the modified form stated "it was easier to read" was "friendlier" and was enhanced by the pictures. Those who preferred the standard form declared it to be "more professional" "shorter" and "more serious."

There have been discussions about the appropriateness of matching the amount of information that subjects prefer to the amount of information provided and their subsequent retention and use of the information. 35 Whether to design ICD's in a one size fits all is an issue that remains unresolved. In an editorial from the Archives of Pediatric Adolescent Medicine, Victoria Miller and Robert Nelson #24 discuss Tait's research and conclusion. The point is raised that understanding did not affect the parent's decision to provide consent. This causes a re-visit to the idea that disclosure of information and

understanding may have only a small influence on decision making. They emphasized that other variables are important and include the way in which the information is used in actual decision making and personal factors and beliefs about research and the extent that the decision is made voluntarily.

Miller and Nelson cite prior research that suggest a match between the subject's desire for information and the level of information that is provided decreases anxiety and increases coping and conclude that the consent document is only a part of a complex "set of individual, interact ional and situational variables."

IRB's & Templates

Cardinal writes that is should not only be written to conform to IRB standards, but should foster true understanding by the potential research subject. 32 He laments that it may be easier to write to obtain IRB approval then to achieve understanding. Dr Paasche-Orlow and others have demonstrated that even consent forms developed or approved by Internal Review Boards frequently exceed their own readability standards. Indeed, they may have an inadvertent role in "promulgating unreadable" consent forms. 31 Philipson et. al #21 reviewed informed consent forms and found that of the 76 forms they evaluated, none had Fry scores or readability and process ability (R&B) scores in the target range. Ninety-six percent had readability levels higher then the recommended grade (8th)
Goldstein et. al found similar dismal results. Of 284 forms they analyzed the average reading level was high 12.2 (12th grade) less than 10% were written at a 10th grade reading level or below. All these forms were submitted to and approved by university IRB's. Their conclusion-"poor readability occurs in all university conducted research" #21
Hochhauser and others have repeatedly found that documents are written at unacceptably high "college" reading levels #21 and Sports

An example is the attached Informed Consent Template designed and approved by the University of Michigan that demonstrates a 12.5 grade level by Flesch-Kincaid and an Ease score of -----.Ease is described as the overall readability. Higher Ease scores are more desirable. Informed Consent documents should achieve a minimum of 60-80, and aim for over 80.

Important Measurements /Understanding and Comprehension

It is a delicate matter to decide whether a patient has more than the minimum acceptable level of understanding, in order to claim that informed consent has been obtained. 35 Some researchers hold the view that gaining informed consent is impractical - how can we ever be sure what participants understand?

To determine if consent was truly informed, we need to ask if there was sufficient understanding, and if there was any coercion, either explicit or implicit. Barclay / Kerridge Kuczewsi state that informed consent occurs in the context of a social process that is influenced by many factors. His group says that the process of informed consent is influenced by the individuals and organizations that are important to the potential research volunteer, including support groups and the primary healthcare provider. #2

According to Agard, "A real picture of patients' understanding can be obtained by asking them about information previously given and about their beliefs and concerns. If not adapted to match patients' capacity to comprehend information, the consent process can be regarded as a meaningless ritual designed to ensure that physicians or investigators avoid claims of negligence." 51 he continues quoting Gammelgaard, the threshold is that individuals should feel they are able to make a free decision about study participation.

Tips to Improve Comprehension

Wording & Language
Use wording that is familiar to the general public, including language that is concise and straightforward.33

Translation

Oral and written translations are only part of the process of presenting informed consent information to non-English-speaking persons. It is strongly recommended that when forms are translated that they be translated into the subject's language and then translated back into the original language by someone unfamiliar with the original. ( )
Consent documents should also be adapted to the needs of individuals with limited literacy skills and those who are vision impaired. A single research trial may require several versions of the informed consent *document* to tailor the information to a variety of populations.

Format
Use an active voice and personal pronouns 33 41 59
Use a readable sentence structure (micro processing) #22
Ideas should be logically sequenced 41
Use pictures to reinforce written descriptions #22 The first study in Hout's series found that recall of medical instructions averaged 14% but that when pictographs were added to the verbal instruction 85% of the medical instructions were remembered. # 25
Use pictures to show relationships among ideas or relationships 26
Reduce dense paragraphs and increase the type size to 14 points #22
Use headings and bullets 59
Use boldfacing, underlining and column format for reading ease #22
Highlight important points 41

Length
In addition to keeping the sentences and the paragraphs short, keep the overall form as short as possible. 41 59 Teaching the simple concepts first and building to more complex subjects is more effective. High rates of illiteracy are a serious factor in comprehension, but even using standard and simplified consent forms may still result in low comprehension. However, documents that are short, concise and formatted simply are preferable. #2

A CenterWatch Study in 2002 indicated that 14% of volunteers did not attempt to read the consent form before signing and many volunteers admitted to not understanding the risks. #1 Consistently, the literature expresses the same statistics or worse.18% #11 , 35 Lavelle-Jones is quoted on the ahrq.gov/clinic/ptsafety/index website as saying that 69% of patients questions admitted they did not read a consent form before signing it. 49 The National Cancer Institute has said that information that is not required by the Federal Government should not be included in the informed consent. 41 Any examples or definitions should be in supplemental documents or handouts.

Readability
Define medical terms. Check readability statistics. 59 IRB's should require researchers to conduct readability checks prior to IRB submission #21

Patient Advocate
Morreim has advanced a strong case for the use of "patient advocate" to assist and represent the interests of potential research candidates. 55 He suggests that they would be of great value in high stress situations and throughout the research process. A caution he introduces is that care must be taken to avoid creating an adversarial situation.

Time constraints and a host of other factors can likewise intrude. In view of such challenges, some observers have proposed that, at least for some kinds of research, prospective enrollees should have someone - a "patient advocate" or "research subject advocate" - to enhance the process.

Discussion
Research has demonstrated that patient education should include written information to reinforce verbal discussion. #11 It would appear that the converse is true, written information should be accompanied by a discussion between the healthcare provider and the potential research subject. #22 Discuss the ICD thoroughly with the subject. Use the ICD as a teaching tool. Review each section with emphasis on sections that are considered essential (45CFR 46.116) or that the volunteer may have questioned. Use a post-test approach and ask subjects to re-state what you have told them (#11 # 30 43 49and provide immediate feedback. Test questions such as those used by Cardinal 32 will give a good overview of the

subject's knowledge. Emanuel strongly supports the extended 'discussion', but admits it is labor intensive and more complicated. 57

Video and multimedia tools
While there is ongoing discussion, without consensus, 50 53 about the effectiveness of videos to improve the comprehension of subjects considering research participation,"Entering Clinical Trial: Is it Right for You?" received the Health Improvements Institute's Award for Excellence in Human research Protection for Innovation. Responding to public opinion that prospective research participants may not understand information disclosed to them in informed consent documents, Flory and Emanuel undertook a MEDLINE search (including dates 1966-2004) to review the literature on interventions to improve participants understanding of information disclosed to them in informed consent documents. They concluded that efforts to use multimedia and enhanced consent forms have had only limited success. "Having a study team member spend more time talking on-on-one to study participants appears to be the **most** effective available way of improving research participants understanding. 28 50

Websites
While providing cautionary reminders that Internet sites are not always reliable, direct potential subjects to websites that refer to the specific condition being studied. University and professional organization sites have more credibility. `i.e. The National Cancer site as well as the Office for the Protection of Human Research (OHRP) and The FDA

Training
In January 2006, Cox et.al. conducted a review that concluded that health care professionals need clear and practical guidelines and training packages to ensure that details of Phase 1 trials are communicated to the potential subjects. 27 17 In a study to Improve documents for children with cancer, Emory University will be directly observing, taping and coding informed consent conferences. They plan to then train their research assistants. 47

Multiple courses are offered to ensure that those individuals entrusted to obtain informed consent are aware of their duties and responsibilities. The University of Michigan offers PEERS training to ensure that all individuals that obtain signatures for Informed consent are adequately trained. The---offers a free online course----------. NIH requires that prior to any funding being released under their grants, critical members of research teams must document that they have received appropriate training.

Two Versions of a Written Informed Consent Document

The template that is provided by the University of Michigan (appendix) contains wording that is required, both to ensure that the essential elements are included in every Informed Consent Document and to ensure that the institution has their liability minimized. That language is scored as a Grade level 10.4 with an Ease score of 50.1 on the Microsoft Word version of the Flesch-Kincaid Grade level tool and the Flesch Reading Ease tool.

Informed Consent Document #2 was developed and subsequently approved by an academic institution IRB in November of 2003 for a complex study looking at blood pressure in individuals with kidney disease. Overall this document had an 11.5 grade level and reading ease of 45. Well above the most generous recommended Grade level (below 8th) for reading and well below the 60-80 Ease score considered adequate. Specific portions of the Informed Consent document considered critical elements for the potential participants were also above the recommended levels. Only the information that was added to the template was included in this scoring, leaving the template language outside the checked language. The purpose section scored a 12th grade reading level and a 38.6 Ease score. The participants section which detailed who could and could not participate scored a 12th grade level and an Ease score of 27.5. The procedures section which describes what will happen to the participant scored a 12th grade level and 43.5 Ease score. The section explaining how much time was required did somewhat better with a 10th grade reading level and a 50.5 Ease score. The risk section, arguably the most critical for the potential subjects understanding for decision making scored a 12th grade reading level and a 36.3 Ease score. These rather dismal scores reflected the scores of other academic institutions and supports ---------- findings.

Informed Consent Document "E" is a revision of Informed Consent Document #2. Revised and subsequently approved by the same IRB in November 2004. Overall this document had an 8.6 grade level and reading ease of 56.9. Not great, but significantly better. Specific portions of the Informed Consent Document considered critical elements for the potential participants were analyzed. Again, only the information that was added to the template was included in this scoring, leaving the template language outside the checked language. The purpose section scored an 8.9 grade reading level and a 63.4 Ease score. The participants section which detailed who could and could not participate scored a 9.5 grade level and an Ease score of 45.7. The procedures section which describes what will happen to the participant scored a 7.4 grade level and 65.0 Ease score. This reflects an enormous increase in the readability appropriateness in a critical area. The section explaining how much time was required received an 8th grade reading level and a 55.8 Ease score. The risk section, arguably the most critical for the potential subjects understanding for decision making scored an 8th grade reading level and a 59.7 Ease score.

Additional changes to the form included an increased font size, the use of columns in the inclusion/exclusion (participants) section, the use of bolding, increased white space and highlighting in the procedures and the risks sections. Simplified sentences were used throughout and medical terms were changed to descriptions whenever possible.

The process was changed to provide the potential participant with a printed copy of the form a week prior to visiting the clinic and phone calls were made to inquire about the patients concerns, questions and understanding during that week. During the clinic visit, the potential subject was shown pictures of the equipment and given non-institution, written information about being a study research participant.

We found that a greater number of potential subjects decided not to participate in this moderately high risk study, but those that did participate all stated that they were glad that they had entered the study and would consider other research studies in the future.

National Response to the Issues

Funding for Research
In September of 1996, the NIH Office of Extramural Research (OER) announced a special Request for Applications (RFA) focusing on Informed Consent Research Involving Human Participants. The goal of this initiative was to identify and validate methods for improving the informed consent process in scientific research Response to the RFA was remarkable, resulting in the submission of 82 applications by the March 11, 1997 deadline. 54

The University of Michigan received a $1.5 million dollar grant to improve the informed consent process for clinical researchers and study participants. The study includes lectures, workshops, small group discussions and role playing to improve clinician's skills.

FDA
FDA has responded by widely publicizing their information website, specifically ones that relate to testing products in people. 39

Patient Advocates
In 2001, the National Center for Research Resources (NCRR) of the National Institutes of Health (NIH) established a network of Research Subject Advocates (RSAs), located in the NIH's 82 General Clinical Research Centers (GCRCs). The NIH funds these GCRCs with five-year grants supporting some 7,000-10,000 active protocols, and now requires at least one RSA at each Center compliance-oriented functions 55

The National Cancer Institute
The National Cancer Institute has released new guidelines designed to make the forms more useful, aid investigators in developing better documents and assist IRB's in their review. 40

Templates
Responding to concerns that ICD's were to long, complicated and hard to understand several national as well as private and academic groups have developed templates. (Appendix__)Among them, the National

Cancer Institute (NCI), along with the Office for Protection from Research Risks (now the Office of Human Research Protections) and the U.S. Food and Drug Administration, formed an Informed Consent Working Group. A consent form template was created that includes all of the federally required elements for the document, including explanations of the research procedures, related risks and possible benefits, alternatives to participation, and the rights of research participants. 41

Conclusion

While following all the recommendations for improving the paper informed consent document will undoubtedly result in some improvement in patient/subject understanding and their ability to make a personally appropriate decision regarding their participation in research, the real world situations make a boiler plate system of informed consent form unrealistic. The most promising outcome would be a transition from what Greg Koski, calls a Culture of Compliance to a Culture of Conscience and responsibility. #1 If, it is indeed true, that the great majority of research team members are well-intended people who are driven by concern for their patients and a desire to learn the best methods to care for them it is possible that defining the ethical behaviors that are expected in our society and encouraging all interested parties to participate in the public debate over the issues that confront clinical research will result in a system that both protects the patient and advances science. Given the academic, financial and medical pressures on the research system, if we do not move the debate into intense public view, encouraging both providers and patients to take part we risk continued experimentation and take the chance that some practitioners will not think that the rules apply to them. It is very expensive to ignore the past.

"Every investigator must do the right thing because it is the right thing to do."
Ernest d. Prentice, Ph.D. January 25, 2006

The ethical approach to experimentation in man has several components: two are more important then the others, the first being informed consent…..Secondly, there is the more reliable safeguard provided by the presence of an intelligent, informed, compassionate, responsible investigator Henry Beecher, 1966 37

Appendices

Timelines of Inappropriate Research and Experimentation
United States Government Guidelines
Templates for Informed Consent Documents
University of Michigan
Sport Science
Stanford

Web Links
- 45 CFR 46.116 Essential Elements of Informed Consent
- Belmont Report
- Words to be used as substations for medical terms
- Code of Federal Regs
- Nuremberg
- Common Rule

Informed Consent Documents
- University of Michigan Request and Consent for Medical, Surgical, Radiological and Other Procedures
- Informed Consent Document #2
- Informed Consent Document "E"
  - Graphs
  - Data

Informed Consent pamphlets
- OHRP
- University of Michigan

References