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Monetary inducement to participate in research

William Ewing Palmer
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ABSTRACT

Most ethical codes and regulations forbid excessive payment of normal, healthy research subjects. Ethical concerns center on the capacity of vulnerable subjects to refuse the temptation of excessive, or undue, monetary inducement and to protect themselves from the risk of injury in participation in research. Subjects most vulnerable to offers of money include impoverished persons who lack sufficient economic resources to purchase basic necessities and who lack viable options for employment. In this discussion, criteria are identified for distinguishing due from undue monetary inducement to participate in research. Applying fundamental ethical principles, a systematic analysis of criteria such as impoverishment of subjects and research risk leads to the conclusion that size of payment by investigators should be unrestricted except in research presenting the highest acceptable risk.

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A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Medicine

by
William Ewing Palmer
Class of 1984

PREFACE

As a Chemistry major at Georgetown University, I designed a solvent system for synthesizing organic polymers. In the process, I spent two years weighing reactants, distilling solvents and purifying and characterizing polymeric products. I made scientific hypotheses, constructed data tables, plotted curves, calculated chemical structures and predicted the results of future research.

During a fellowship and, perhaps, afterwards, I will be back in the laboratory doing basic science research. Eventually, I plan to devote significant time and effort to clinical research.

In between, while at medical school, I have appreciated the opportunity provided by Yale's thesis requirement to make a philosophical analysis of ethical issues in research involving human subjects. By balancing an understanding of ethical and scientific standards in human investigation, I hope to enhance both my care of patients and efficacy in research.

I obtained my introduction to and interest in the ethics of clinical research during four years on Yale's Human Investigation Committee (HIC). Special thanks go to Robert Levine, chairman of the HIC, for sharing with me his experience and expertise.

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INTRODUCTION

Most ethical codes and regulations forbid excessive payment for participation in research.[1] None, however, specify a sum of money less than which is a "due" inducement and more than which is an "undue" inducement. The latest Department of Health and Human Services (DHHS) regulations (1981) state only this instruction to Institutional Review Boards (IRBs) for approval of research employing persons vulnerable to offers of money: "Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, [IRBs shall require that] appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects."[2] Beyond this vague reference to "appropriate additional safeguards," there are no guidelines to aid IRBs and investigators in determining what payments to subjects are excessive. There are no detailed instructions for restricting monetary inducements.

My objective in this discussion is to identify criteria for distinguishing due from undue monetary inducement to participate in research. These criteria are evaluated by considering the historical, legal, philosophical and scientific developments that have affected research involving human subjects.

I define and contrast terms such as research and experiment, coercion and manipulation, autonomy and beneficence. Research carried out in Germany during the Hitler regime exemplifies the worst kinds of abuses of research subjects and signifies the starting point for the evolution of modern day's ethical codes and regulations. I consider: the publication in the 1950's of research involving disadvantaged subjects; the role of voluntary, informed consent research subjects and institutional review of research protocols; the fiduciary relationship between physicians and patients versus investigators and subjects; the vulnerability of impoverished persons who consent to participation in research because of the opportunity to earn money; and the example of prisoners as a class of persons with maximum constraints on their options for earning income. Finally, considering normal, healthy persons who are not prisoners, I use this background information to identify various criteria for distinguishing due from undue monetary inducement. A systematic analysis of these criteria suggests ways for investigators and IRBs to evaluate the potential for undue inducement of vulnerable subjects to participate in research.

EVOLUTION OF RESEARCH INVOLVING HUMAN SUBJECTS

Before World War II, courts ruled infrequently on cases of failed medical therapy. Juries condemned treatments that deviated from established medical practice and called them "experiments." These "experiments," what would be considered malpractice today, usually involved a single patient who was unaware that anything new was being tried.[3] *In court, most physicians defended their unorthodox practices by calling them "innovative therapy." Some of these physicians tried "innovative therapy" as a last resort effort and with the best of intentions but still were found guilty of "experimenting" and liable for patient injury.*[4]

In New York in 1871, a jury held a physician liable for unsuccessful treatment of a dislocated elbow because he did not give standard medical advice about immobilizing the joint with a sling. In defense of his silence, the physician claimed that he should be able to try new modes of therapy. What today's court would recognize as gross negligence, the court then called an exercise in "experimentation." It ruled:[5]

> *If the case is a new one, the patient must trust to the skill and experience of the surgeon he calls; so must he... [if] there is no established mode of treatment. But when the case is one to which a system of treatment has been followed for a long time, there should be no departure from it unless the surgeon who does it is prepared to take the risk of establishing, by his success, the propriety and safety of his experiment.*
>
> *The rule protects the community against reckless experiments, while it admits the adoption of new remedies and modes of treatment only when their benefits have been demonstrated...*

In Missouri as late as 1926, a physician tried an unproven infectious agent to cure hemmorhoids. The result: for the patient a rectal ulceration and for the physician the court's condemnation as an "experimentor." The judge ruled that: "Failure to employ the methods followed or approved by [the physician's] school of practice evidences either ignorance or experimentation on his part. The law tolerates neither."[6]

These cases involve medical practice, not research, and emphasize the importance courts placed upon established medical procedure. The burden of proof was upon the "experimentor" to show that his "experiment," whether innovative therapy or quackery, was supported by some reasonable theory. Concern for patients' choices was rarely mentioned in court decisions. Rather than requiring the consent of patients (subjects), courts protected patients' interests by enforcing what were considered to be strict standards of medical practice.

During World War II, research protocols, with or without therapeutic components, expanded to employ larger, more diverse subject

populations. With development of statistical theory to support double-blinded and randomized assignment of subjects to control groups, society acknowledged the significant benefits obtained through research involving human subjects. Human investigation became accepted. Enthusiastic public support resulted in exponential increases in funding. Between 1945 and 1965, yearly expenditures for human investigation at Massachusetts General Hospital increased 1700% to 8.4 million dollars; during the same period at the National Institutes of Health, annual expenditures for research increased 62400% to 437 million dollars.[7]

Parallel with these benefits, however, examples of exploitation of research subjects received widespread publicity. The legitimacy of clinical research was reevaluated and its accountability was questioned. Public hysteria over a perceived potential for physical and psychological torture of research subjects began with the notorious, coercive practices of Nazi physicians during World War II. These heinous crimes committed against war prisoners focused philosophical concern on subjects' consent to participation in research. In 1947, in response to these crimes, the Nuremberg Code established the ethical groundwork for future codes on human investigation. Governmental intervention was the inevitable next step with regulations requiring approval of research protocols and review of consent procedures by federally mandated committees.

DEFINITIONS

Conceptual errors in the nomenclature of research ethics are perpetualized during medical education and through scientific seminars and journals. Before elaborating on the historical events contributing to present day regulations, and before continuing with a discussion of vulnerable classes of persons, the meanings of such terms as research, practice and experimentation, as well as coercion, manipulation and inducement need to be clarified. During the 1970's, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) attempted to clarify the nomenclature of research ethics. The Commission standardized basic terms and identified fundamental ethical principles before conducting its comprehensive investigation of research involving human subjects. This investigation culminated in the development of guidelines on the protection of research subjects and policy recommendations for the Department of Health, Education and Welfare (DHEW) - now the Department of Health and Human Services (DHHS).

Research and Practice

In 1972, Thomas Chalmers restated the misconception established in earlier court decisions confusing research and practice: "It is extremely hard to distinguish between clinical research and the practice of good medicine. Because episodes of illness and individual people are so variable, every physician is carrying out a small research project

when he diagnoses and treats a patient."[8] *This misconception, held by most physicians, is important to articulate and to clarify because it causes physicians to treat patients and subjects similarly when actually they have different needs and rights. In defining the terms research and practice, the Commission proposed that there were important distinctions between the goals of carrying out a reasearch project and those of treating a disease.*

"Research" refers to a class of activities conducted to generate data through scientific observation. Its purpose is to develop generalizable knowledge and to test hypotheses, principles and scientific relationships.[9]

"Practice" refers to a class of activities conducted solely to enhance the well-being of an individual patient. Its purpose is to provide diagnosis and therapy with a reasonable expectation of success.[10] *Hans Jonas asserted: "In the course of treatment, the physician is obligated to the patient and no one else. He is not the agent of society, nor of the interests of medical science, the patient's family, the patient's co-sufferers, or future sufferers from the same disease. The patient alone counts when he is under the physician's care."*[11]

"Experimentation" equaled quackery in early malpractice trials. Semantic confusion between "experimentation" and research explains why the public has continued to place negative connotations on research

involving humans. According to Levine, who served as special consultant to the Commission, "experimentation" refers to a class of activities in which something is tested or tried with uncertain results.[12] *An "experiment" refers ambiguously to either practice or research since both involve activities conducted with inherently uncertain results. In medical practice, for example, a physician will try different dosages of an approved drug in the interest of treating his patient. In research designed to study the efficacy of an unapproved drug, specific procedures prevent similar adjustment of dosages and, therefore, restrict the experimentation typical in routine medical diagnosis and therapy.*[13] *This "deprivation of the experimentation ordinarily done to enhance the well-being of a patient is one of the burdens imposed on the patient-subject in a [randomized clinical trial]."*[14]

Another class of activities called "innovative therapy" illustrates the subtle contrasts between research and practice. An innovative procedure, whether diagnostic, prophylactic or therapeutic, is designed solely to enhance the well-being of an individual patient. In this sense it is conducted in the context of medical practice and not research. Although it may be done routinely, an innovative procedure has not been sufficiently tested to determine whether it meets the standard of having a reasonable expectation of success.[15] *Without sufficient data to permit a prediction of its safety and efficacy, an innovative procedure should be made the object of a research project. In this project, however, the therapeutic objectives should not be compromised by the research objectives. Since these two objectives are*

always opposed, "therapeutic research" is nonsensical terminology. A systematic collection of data does not in itself benefit patients/subjects.

The Commission made these clarifications on "innovative therapy:"[16]

> *When a clinician departs in a significant way from standard or established practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.*

It has been suggested that a better designation for "innovative therapy" is "nonvalidated practice."[17] *"Practice" is more accurate than "therapy" because diagnostic and prophylactic procedures (practices) are meant to be included in the definition along with therapy. "Nonvalidated" is more accurate than "innovative" because a practice may be new (and therefore innovative) or it may be standard and routine but without sufficient testing to merit a prediction of its safety and efficacy.*

Ethical Principles

Ethical principles are fundamental in justifying or challenging judgements about biomedical research involving human subjects. They are implicit in ethical norms which indicate how the ethical principles should be applied (i.e., whether actions should or should not be done). Professional codes and federal regulations are collections of ethical norms. In addition to these collections, however, the codes and regulations include procedural guidelines detailing how to implement the norms in directing and judging the conduct of investigators.

Three fundamental principles are relevant to the ethical codes and regulations on research involving human subjects: respect for persons, beneficence and justice.

Respect for Persons: As the 18th century philosopher, Immanuel Kant, wrote: "So act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as a means only." Two precepts are derived from Kant's imperative. According to the first precept, respect for persons is intimately connected with freedom and liberty and is often interpreted as creating a duty to treat persons as autonomous. Autonomous persons are self-determining, make their own choices and protect their personal interests. They should be free to decide who tresspasses, and when, on their bodies. They should not be interfered with unless they agree to it. Therefore, autonomous persons who are potential research subjects should deliberate about the procedures, alternatives, and harms and benefits of a protocol and should be responsible for their decision to

participate. Complete disclosure of information about a research protocol should override any concern for harm that might occur as a result of the disclosure. Autonomous persons do not need protection.

According to the second ethical precept, respect for persons requires that "...persons with diminished autonomy are entitled to protection."[18] *For example, persons who are dying or incarcerated not only need but also are entitled to protection from harm. Protection of autonomy does not mean that persons with diminished capacity for decision-making should be absolutely prohibited from participating in research. Instead, these vulnerable persons should protected against treatment as means to others' ends by maximizing their capacity to negotiate a voluntary, informed consent and to refuse to consent to participation.*

Beneficence: The principle of beneficence originates in one of the oldest and most quoted of medical maxims: "As to diseases, make a habit of two things - to help or at least to do no harm."[19] *Hippocrates specified the duty to do good, beneficence, and the duty to do no harm (primum non nocere), nonmaleficence. He directed that physicians voluntarily assume certain moral duties through their special relationship to sick persons. On top of the universal obligation of passive noninfliction of harm on others, they should actively prevent and remove harms.*

The Commission gave nonmaleficence a high priority in its definition of beneficence:[20]

> *The term, beneficence, is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: 1) do no harm and 2) maximize possible benefits and minimize possible harms.*

In the context of biomedical research, beneficence requires that physicians promote the health and welfare of not only present but also future patients. Physicians should conduct research involving human subjects because its goal is to develop information about the prevention, diagnosis and treatment of disease. But there remains the obligation to "do no harm." Beneficence cannot justify promotion of societal benefits through research that intentionally injures subjects. However, it can justify intentional exposure of persons to the risk of injury when those persons choose to accept that risk to benefit themselves or others.

Justice: The principle of justice can be understood through a concept of fairness. Justice is done when a person is given what he is due or owed. A person is treated fairly when he gets what he deserves or can rightly claim.[21] *The term "justice" in this essay will be confined to mean "distributive justice," the fair sharing of social benefits and burdens. Justice has not been done when a class of persons is selectively denied a reward, service or opportunity (e.g., the chance*

to participate in research) to which there is an equal entitlement with others. Likewise, a class of persons is treated unfairly when it assumes more than its fair share of society's burdens. Since society at large enjoys the benefits of research, all citizens should share in assuming its burdens.

Justice has important implications in considerations of who should or should not be free to consent to participation in research. Essential to distributive justice is this principle attributed to Aristotle: "Equals ought to be treated equally and unequals unequally."[22] *If two classes of persons are equal in relevant respects, then both should share equally the burdens of participation in research. If two classes of persons are unequal in relevant respects, then they should be considered as potential research subjects in proportion to their differences.*[23] *Likewise, no class of persons should be denied the right to participate in research unless its differences are relevant to the denial. But what differences are relevant? What criteria should determine relevance? Should such criteria include good or poor health, past or potential accomplishments, social worth, legal status, religion, income, race, age, sex, or I.Q.?*

The Commission derived certain recommendations from the principle of justice. It concluded that rules and regulations would be unjust if they failed to make relevant distinctions between classes of persons. Biomedical research should not be an utilitarian endeavor justified in creating the greatest benefits for society by using only convenient and

disadvantaged persons as research subjects. The Commission interpreted fairness as requiring protection of research subjects against abuses from investigators - even if this protection resulted in fewer medical benefits for society as a whole. A fair sharing of benefits and burdens requires special protection of disadvantaged persons. Addressing problems in the fair selection of subjects, the Commission recommended that:[24]

> *... the selection of subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.*

Coercion, Inducement and Manipulation

Intervention by one autonomous person in the actions of another needs justification when the intervention limits freedom of choice. The broad range of possible interactions between persons establishes a continuum at the far ends of which are coercion and persuasion. As usual with extremes, coercion and persuasion generally pose no ethical dilemmas. The relevant ethical principle, respect for autonomy, is easily, effectively engaged. Because respect for autonomy embodies freedom of choice, coercion is unjustified and persuasion is justified. Between them on the continuum are manipulation, bribery, and offers of

inducements. These interventions, discussed shortly, often pose ethical dilemmas - especially in biomedical ethics - and may or may not be justified depending on which ethical principle is considered to be most pertinent.

Coercion: Coercion denies personal liberty and freedom of choice and rarely is justified in dealings with autonomous persons. Whereas logic is the means by which rational persons persuade one another to a given course of action, coercion requires a threat.[25] *One person coerces another by explicitly intending to bring about harmful consequences unless there is cooperation. To be coerced, a person must understand the consequences of the threat and act in large part to avoid those consequences. A threat is not coercive if a person would have acted in the same way in its absence. A coerced person recognizes that he is worse off if he suffers the threatened consequences than if he avoids them. For example, a physician coerces his patient to participate in research if he deliberately makes hospital admission and standard medical therapy contingent upon consent to participation in a research project.*

Inducements: Inducements are incentives and do not constitute threats. Whatever his interests, urges and weaknesses, the person who accepts these offers is not coerced. But offers are made, like threats, in order to alter another's behavior by changing the consequences of acting one way or another. Nozick has suggested a simple way of

distinguishing between offers and threats.[26] *If the consequences of the new act are improved over the natural and expected course of events, they constitute an inducement; if the consequences are worsened, they constitute a threat. Likewise, an inducement is offered if a person prefers engaging in the new act (because of the improved consequences) to the old one; however, a threat is made if a person prefers engaging in the old act (except for the worsened consequences) to the new one. The presence of an individual's willingness or unwillingness to alter behavior marks an important difference between inducements and threats.*

Inducements can take various forms, e.g., money, material reward, medical therapy, escape from boredom, friendly attention, curiosity, et cetera. They can be unethical without being coercive. Beauchamp, a bioethicist at the Kennedy Institute of Georgetown University, asserts that "...undue influence occurs whenever someone uses an excessive reward or irrationally persuasive technique to induce a person to a decision the person might otherwise not reach."[27] *Nozick concurs in stating that: "A person can be gotten to do something which someone else wants him to do, which he otherwise wouldn't do, by offers as well as by threats;" he adds that: "...sometimes an offer is so great that a person cannot reasonably be expected not to go along with it..."*[28] *A monetary inducement to engage in a particular act may be so great that a person does not make his own choice. The decision is made, in this instance, by the payment. The payment is undue and unjustified if it violates the principle of respect for persons by causing the will of*

another to predominate and by treating a person as a means rather than an end.

In the context of research, for example, investigators offer a substantial inducement to patients if they promise to waive hospital fees in return for written consent. This fee waiver is undue inducement if it impairs the ability of "volunteers" to weigh the risks of the research against the benefits. Besides money, undue inducements may include medical therapy. Terminally ill cancer patients are offered undue inducements to participate in research if they ignore disabling side effects of a highly toxic investigational drug because physicians, honest but perhaps unrealistic in their enthusiasm and optimism, present the unproven chemotherapy as probably curative.

Manipulation: Manipulation requires greater psychological sophistication and subtlety compared to the crude threats of coercion.[29] *Coercion and inducements are open about seeking to influence behavior, whereas manipulation is more devious about it. Like coercion, however, manipulation limits a person's freedom of choice, his sphere of autonomy, and treats him instrumentally - as a means rather than an end. This limitation involves either deceiving persons, taking advantage of their weaknesses or both.*

Deception violates autonomy because truthful communication is essential to decision-making. Patients, for example, deceive physicians by exaggerating and creating symptoms and manipulate them into

mistakenly prescribing more and stronger drugs. The duty of veracity is part of the respect that physicians owe patients and research subjects. Deception violates this respect because either absence of information (silence) or incorrect information (lies) put persons at risk of injury by preventing them from realizing possible harms and protecting themselves. Physicians-investigators, for example, manipulate patients by deliberately refraining from telling them about alternative treatments in order to secure their participation in a protocol.

In clinical practice, physicians may employ deception when patients have diminished autonomy and when the principle of beneficence justifies therapeutic privilege (therapeutic privilege may be called benevolent deception or paternalism). For example, physicians can be justified in deceiving a dying patient when they do not explain the critical nature of an illness so that the patient maintain a psychologically healthy outlook. In medical practice, the Hippocratic Oath does not oppose this kind of misrepresentation. In medical research, however, deception is rarely justified except in some behavioral studies.[30]

Manipulation can also involve taking advantage of others' perceived weaknesses.[31] *Investigators take advantage of the physician-patient relationship and patients' dependency when, if patients do not want to consent to participation in a research project, investigators act in an angry or disappointed fashion. Since investigators know that patients will probably find the pressure*

irresistable, they are taking advantage of patients' vulnerability. Referring back to the example of the waiver of hospital fees, if the investigator purposefully offers a tempting monetary incentive because he knows his patient needs money, he not only provides inducement to give consent, but also manipulates that patient into giving consent. In addition to manipulation, this combination of monetary inducement and poverty constitutes bribery.[32]

HISTORICAL CONTRIBUTIONS TO INFORMED CONSENT

> *"...prisoners were used just as rats, guinea pigs and rabbits are used in the laboratory and sometimes without showing them as much consideration as we show our animals in the laboratory."*[33]

With these words in 1947, Andrew Ivy, a physician who consulted for the U.S. Naval Bureau of Medicine and Surgery and who testified as an expert witness at the Nuremberg Military Tribunals, described the treatment of participants in "experiments" to develop a typhus vaccine. The protocol, designed by Nazi physicians, required the injection of blood from prisoners with acute typhus fevers into other prisoners who fell into one of three groups: 1) the unvaccinated control group, 2) the vaccinated group (the German vaccine was already known to be ineffective compared to the American vaccine), and 3) the "passage group," used to keep the vaccine alive, virulent and readily accessible. Most participants had been already threatened with execution. Many of them died with acute typhus infection. Ivy continued: "The crux of the ethical question pertaining to the Nuremberg trial from the medical viewpoint is whether condemned prisoners should be experimented on without their consent. ...My answer to that question is no."[34]

At the Nuremberg trials, similar physically and psychologically torturous "experiments" were defended by the Nazi physicians in the name of medical research and societal benefit. Although the so-called investigators were prosecuted for committing barbaric war crimes (albiet under the directive of higher Nazi authorities), these war crimes were

considered by the Nuremberg Military Tribunal to represent compelling examples of the potential for abuse of subjects in modern biomedical research. Since no ethical or legal standards existed by which the physicians/researchers could be judged, a set of rules were developed for the Nuremberg Military Tribunal. These ten rules became known as the Nuremberg Code.

In spite of the heinous nature of the torture conducted by physicians, the Nuremberg Code did not condemn most types of future medical research. Some of its rules, if restrictive by 1940's standards, articulated in simple terms a minimum standard that is taken for granted today. For example, Rule II specifies that acceptable research involving human subjects must "...yield results for the good of society that are unprocurable by other methods...". This research must be "...based on the results of animal experimentation..." (Rule III), must be "...so conducted as to avoid all unnecessary physical and mental suffering and injury" (Rule IX) and must be "...conducted only by scientifically qualified persons" (Rule XIII).

The first rule of the Nuremberg Code makes the most significant contribution to the ethics of research involving human subjects. It provides the definition of informed consent that has been used in all subsequent codes and regulations:[35]

> *The voluntary consent of the human subject is absolutely essential.*
>
> *This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.*

This first rule provides a definition of informed consent that is rigorous in its requirements and includes four essential elements: valid consent must be competent, informed, comprehending and voluntary.

Informed consent and its elements are primarily justified by the principle of respect for persons. In case law as well as medical ethics, informed consent provides a framework for judging whether physicians have fulfilled their duty to respect autonomy. In a classic opinion, Supreme Court Justice Cardoza gave the operational definition of autonomy: "...every human being of adult years and sound mind has a right to determine what will be done with his own body..."[36] *In research as well as medical practice, autonomous persons possess both legal and ethical rights to self-determination. Through informed consent, patients-subjects protect their own interests by deciding whether or not to expose their body to the risks of participation in a research project. They should obtain a thorough understanding of the*

relevant information about procedures, alternatives and possible injury and should be able to weigh for themselves the risks of participation against the benefits.

Elements of Valid Consent

Competence to consent: Competency is more a precondition of informed consent than an element of informed consent.[37] In biomedical research, competency means legal competency. Infants, children, the mentally retarded and the comatose include persons who are legally incompetent to give informed consent because of immaturity, legal status (e.g., seventeen year olds who are able to understand information), mental retardation or neurological damage. Whereas competent persons make reasonable decisions based upon rational deliberation, incompetent ones, except for the special case of older children, lack the capacity to comprehend information and to act voluntarily (two of the other elements of valid, informed consent). Although incompetent persons cannot make their own choices about participation in research, some of them need specialized medical care that can be developed and improved only through research involving them. Since incompetent persons have no autonomy, the principle of beneficence requires that guardians protect them from participating in research that may be harmful. When infants, for example, must be research subjects, parental or guardian authorization is mandatory.

Disclosure of Information: Rule I of the Nuremberg Code specifies that a research subject should know "...the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment." Although their goal is similar, today's regulations require much more detailed disclosure (the specific laws are not relevant, here).

In medical practice, the principle of beneficence can justify a more flexible standard of disclosure than can the principle of respect for autonomy. A physician's duty to protect patients from harm comes into conflict with and sometimes overrides the duty to inform them fully. Therapeutic privilege permits nondisclosure of information that physicians claim probably would cause physical or mental harm to a patient.

In research, the standard of disclosure is based upon what the "reasonable person" (the average of rational lay persons in society) would consider necessary information about a research protocol.[38] *This standard has been established by case law in medical practice and is not different from standards of disclosure in other professions where there is a fiduciary relationship. Disclosure need not approximate the scope and depth of physicians' knowledge about diseases, risks, complications, and statistics. During the consent process, the "reasonable person" standard is satisfied by the minimum of information*

required by the regulations in a consent form. Except for this minimum of information, the investigator has practically no legal requirement to provide individual informational needs (ideally, however, investigators attempt to satisfy these individual needs by answering subjects' questions).

Comprehension of Information: Regardless of the quantity of information presented and how it is presented, inadequate comprehension by potential subjects precludes valid informed consent. Information should be conveyed under circumstances that permit enough time for subjects to weigh the risks and benefits, consider alternatives and ask questions. For example, in a study of new birthing techniques, the informing process should be conducted in advance of the proposed research to avoid coincidence with the onset of labor or the administration of pain medications. In addition, when obtaining the consent of persons with diminished capacity to understand information (e.g., because of limited education or senility), the use of technical language should be commensurate with the intellectual capacity of the subject.

In routine practice, uncomprehending consent can still be valid consent if the physician can justify the use of therapeutic privilege. In research, however, uncomprehending consent violates the principle of respect for persons. Competent patients sometimes hold blind trust in their physician-investigator and refuse full disclosure of information about a research project. Because of their faith, patients may magnify

their vulnerability to participation in research that presents risk of injury and to treatment as means rather than ends. In this situation, physicians-investigators should show respect for subjects'autonomy, whether the risks of participation are minimal or substantial, by imposing the undesired information upon these subjects or foregoing the research. Then, although subjects may study the procedures, alternatives, and harms and benefits and become as informed as the "reasonable person," they may choose to ignore the information and act upon irrelevant, irrational and emotional viewpoints grounded in instincts and intuitions. Obviously, investigators cannot anticipate or prevent unapparent personal or psychopathological motivations.

Uncomprehension of information illustrates the concept of intrinsic constraints and introduces the fourth element of informed consent, voluntariness.[39] *Voluntariness implies freedom to make choices about one's own destiny. A necessary condition of comprehension is that persons possess the inherent, or intrinsic, freedom to make rational decisions. Except for the case of older children, for example, legally incompetent persons possess constraints on this intrinsic freedom. Infants, the mentally retarded and the comatose are constrained by immature or defective neurological circuitry. These neurological constraints on the autonomous, decision-making authority of incompetent persons are intrinsic because they may be objectively evaluated and measured (viz., by neurological testing and mental status examinations). Uncomprehending persons who are not incompetent (e.g., uneducated persons, psychotic and sedated patients) also possess*

intrinsic constraints. In the next section on voluntariness, the objective nature of intrinsic constraints will be contrasted with the subjective nature of extrinsic constraints.

Voluntariness: "The voluntary consent of the human subject is absolutely essential." (Nuremberg Code, Rule 1).

A voluntary decision to participate in research is a free choice made without the influence of coercion, manipulation or undue inducement. These deliberate interventions totally nullify valid consent. On the other hand, the influence of reasonable inducements, pressures or persuasion does not negate voluntariness. Because undue and due inducements to consent to participation fall along a continuum, the factual determination of when consent is not voluntary - when a person is not free to refuse participation - must be made individually and in light of the particular circumstances. In some cases, no sharp boundary can be drawn between inducements that are undue and those that are merely enticing.

Drawing a contrast between intrinsic and extrinsic constraints on voluntariness causes more blurring of this boundary. As described, intrinsic constraints can be objectively assessed and measured. In the case of incompetent persons, intrinsic constraints include immature or defective neurological circuitry. They vitiate the freedom to make choices, the capacity to make rational decisions and the voluntary consent to participate in research. In contrast, extrinsic constraints

include needs, desires, family demands and other pressures that are part of the normal burden of everyday existence. It is the subjective nature of extrinsic constraints that prohibit a predictable assessment of their effect on persons' vulnerability. For example, there may or may not be significant increase in the vulnerability of persons who need more than most other persons or who earn less than the average wage. An evaluation of constraints such as needs and desires must be made individually and without objective determination of the exact degree to which these extrinsic constraints limit the freedom of persons to make rational decisions.

Even in the exceptionally constrained environment of prisons, voluntariness may be preserved enough that consent to participation in research may be valid. Although prisoners possess the neurological capacity to comprehend information and to make rational decisions, there are other constraints on their freedom of choice. Both intrinsic and extrinsic, these constraints do not necessarily negate voluntariness; however, they place severe limitations on it. Intrinsic constraints include, for example, the unavoidable and necessary effects of institutionalization (deprivation of liberty and dependency on authority), as well as impoverishment, inadequate medical care and substandard living conditions. Examples of extrinsic constraints are individual prisoner's boredom and hope for parole. These constraints, although they make participation in research extremely attractive do not imply that the only possible inducements for prisoners undue ones. Constraints as compelling as poverty and hope for parole need not

invalidate voluntary consent to serve in medical research as long as excessive sums of money and reduction of sentence are forbidden inducements.

Historical Developments in Informed Consent after WW II

The Nuremberg Code was intended to provide a basis for international law. In the U.S., however, the legal standing of the N.C., as well as that of other codes of research ethics including the Declaration of Helsinki (1964) and the AMA Ethical Guidelines for Clinical Investigation (1966), remains undefined. In so far as these codes have been adopted by the medical profession as standards of conduct, they can be used to establish researchers' duty and to bring a verdict for a research subject.

In the New England Journal of Medicine, Beecher in 1966 disclosed thirty-two examples of published research involving subjects for whom the consent status was unclear. All of these research projects presented more than minimal risk of injury to the subjects.[40] *His disclosures received widespread publicity and contributed to renewed suspicion of biomedical research involving human subjects. In the shadow of Nazism, each example reminded ethicists and legislators of the possibility of errors in the ethical judgement of doctors conducting otherwise commendable and scientifically valid research. Beecher emphasized that:*[41]

> *An experiment is ethical or not at its inception; it does not become ethical ad hoc - ends do not justify means. There is no ethical distinction between ends and means.*

One year before Beecher's article, the potential for abuses of subjects by investigators came under extensive federal scrutiny and eventually resulted in laws requiring institutional review of protocols and consent procedures to ensure better protection of the welfare of research subjects. Three examples of the kinds of studies that provoked more comprehensive regulation of investigators are presented below:

Jewish Chronic Disease Hospital (JCDH)

In a 1960's study of cellular immunity, twenty-two hospitalized, terminally ill and mostly elderly persons received injections of cells of human cancer tissue. The objective of the study was to gain knowledge about immune defenses against cancer cells; the study was not intended to confer therapeutic benefits. The subjects were told that they would receive "some cells." No investigator mentioned the word "cancer."[42] *Given the unlikelihood of harm resulting from these injections, the investigators felt justified in their lack of disclosure and decided to avoid the possibility of upsetting the patients and causing refusals to participate.*[43] *In addition, they neither presented their study for peer review at the JCDH nor asked the approval of all of the physicians who directly cared for the subjects.*[44] *When brought to court for fraud, the investigators were sentenced to one*

year's suspension of license; upon appeal, their sentence was commuted to one year's probation.

Milledgeville State Hospital (MSH)

During the late 1960's at MSH in Georgia, institutionalized, mentally ill patients were enrolled in research equivalent to today's Phase I clinical trials. Most of these patients were legally incompetent.[45] Investigators intended to generate pharmacological data on the distribution, metabolism and excretion of unapproved drugs and not to confer specific therapeutic benefits. They administered these investigational drugs without obtaining the consent of the patient's guardians, without informing the patients' private physicians and without soliciting institutional review by peers. A subsequent state investigation of staff practices at MSH prompted the Medical Association of Georgia to recommend that future research studies have potential therapeutic benefit to the subjects' physical or psychiatric illness, that guardian's consent be obtained, that clinical psychiatrists be informed of the studies and that an institutional committee review every protocol.

Tuskegee Syphilis Study

In the early 1930's, the United States Public Health Service (USPHS) funded and conducted a study of the natural history of untreated syphilis. The subjects included 400 black, mostly impoverished males

with syphilis and 200 controls without syphilis. The study was terminated abruptly in 1973 only after it came to public attention that investigators had not obtained subjects' consent and that, although participants who died usually underwent autopsies, ongoing evaluation of procedures had not been conducted conscientiously. Through 1973, investigators did not prescribe penicillin to treat either the syphilics or controls who contracted syphilis and even tried to prevent subjects from obtaining outside treatment.[46]

The Tuskagee Study endured until public outrage stopped it. Until 1973, it continued to violate the ethical rules of consent established in the Nuremberg Code and all subsequent codes and regulations. It continued to be conducted by the USPHS in spite of the dramatic impact of cancer cell injections at JCDH and metabolic drug studies at Milledgeville State Hospital for the mentally ill. The Tuskagee Study was not terminated in spite of review by DHEW in 1967 (when all USPHS research programs underwent review) and another review in 1969 which concluded that, although a similar study never would be repeated, the consent of subjects in the existing study still would not be obtained.[47]

FEDERAL REGULATIONS AND INSTITUTIONAL REVIEW BOARDS

> *You think that we may trust implicitly to the humanity of the physiologists? - Absolutely. I know these men; they are just as humane as any other men; and to place these vexatious restrictions upon them is an insult.*
>
> *-- Sir William Osler giving testimony before the Royal Commission on Vivisection about yellow fever experiments conducted by Walter Reed on human volunteers (1906).*[48]

Perhaps because it is true that investigators can only be "as humane as other men," susceptible to similar pressures and demands, the Royal Commission of Great Britain in 1906 should have mandated the first committees to review research involving human subjects.

1953 was the first year when USPHS guidelines formally required committee review of research involving human subjects. For thirteen years, however, these guidelines applied only to intramural research being conducted at the NIH. In 1966, Federal policy extended the requirement of institutional review to extramural research receiving USPHS grants. The purpose of review committees was to assess the judgement of the principal investigator and to protect the interests of research subjects. The Surgeon General signed and circulated this policy statement:[49]

> *This review should assure an independent determination: (1) Of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and the potential medical benefits of the investigation.*

In 1974, DHEW issued regulations (45 CFR 46) requiring that committees called Institutional Review Boards (IRBs) be located in institutions where investigators were conducting research involving human subjects. The primary duties of institutional review did not change: IRBs should balance "...society's interests in protecting the rights of subjects and in developing knowledge that can benefit subjects or society as a whole."[50] *What changed significantly were membership requirements. In 1974, DHEW regulations no longer permitted committees made up entirely of scientists and physicians in the investigators' immediate peer group. These regulations reflected earlier guidelines revised by USPHS in 1969: "...[T]he membership should possess not only broad scientific competence to comprehend the nature of the research, but also other competencies necessary in the judgement as to the acceptability of the research in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance." The addition of non-scientists to committees was intended to help ensure the protection of other non-scientists - the elderly, the poverty stricken, the uneducated - who were included in the most likely populations of potential research subjects.*

The most recent regulatory revisions, passed in 1981, were based upon recommendations made by the Commission in 1978. The Commission used general ethical norms to develop specific recommendations about which bureaucratic duties should be assigned to IRBs. IRBs review protocols to assure that research will be conducted in accord with the ethical standards established by these norms. The Commission employed

the five ethical norms contained in most codes and regulations on research involving human subjects.[51] *Protocols should incorporate: 1) good research design, 2) competent investigators, 3) equitable selection of subjects, 4) a favorable balance of harm and benefit, and 5) informed consent.*

IRBs devote unequal attention to each of the ethical norms. IRB's evaluate research design and competency of investigators to the extent that these factors influence the harm-benefit ratio of the research. The duty to evaluate scientific design is usually delegated to the funding agencies.[52] *In addition, IRBs spend relatively little time deciding whether subjects will be equitably selected except when reviewing protocols involving obviously vulnerable populations (e.g., prisoners and the mentally ill).*[53] *Instead, the greatest efforts are devoted to defining the balance of harm and benefit and to ensuring voluntary, informed consent. The information in protocols about research procedures and precautions combined with the expertise of IRB members should provide adequate resources to make a consistent and accurate assessment of the harm-benefit ratio. Guaranteeing voluntary, informed consent, on the other hand, remains a most elusive goal in spite of the attention given to it and the emphasis placed upon it.*

Determination of Voluntary, Informed Consent

Since World War II and the Nuremberg Code, voluntary, informed consent of subjects to participate in research has been the primary

concern of ethicists and legislators. Because IRB members do not intrude upon the privacy of the investigator-subject relationship and do not oversee directly the completeness and comprehension of information and the voluntariness of subjects' consent, the consent form is the primary mechanism by which IRBs attempt to assure valid consent; however, it also may be the weak link in the chain of events connecting IRBs to valid consent. IRBs often become caught up in conforming to the letter of the law and in satisfying specific regulations concerning documentation of informed consent. A disproportionate regulatory burden on consent forms reinforces IRB concern with a tool that by itself cannot ensure voluntary, informed consent. IRBs may spend more time rewording consent forms than reviewing investigators' plans to negotiate consent.[54]

Because even IRB members may confuse their ethical and legal responsibilities, the differences between voluntary, informed consent and legally valid consent (embodied in a signed consent form) need clarification. Voluntary, informed consent functions to show respect for subjects' rights to make choices and to protect themselves. The consent form contains only the minimum amount of information that should be presented to prospective subjects and, at best, should serve as a guide for investigators in their negotiations with subjects. The consent form cannot accomplish the objectives of an appropriate communication between physicians and subjects. In fact, if the consent form is used as the only source of patients' information and comprehension and not as a minimal guide for fuller consent, then it

acts to antagonize and defeat the physician-patient relationship (this special relationship is described in the following chapter). It diminishes the spirit of consent by encouraging investigators to collect signatures.

Documentation of consent on consent forms, like the signing of a commercial contract, also functions to protect the investigator and his institution against legal liability should a subject claim that he was not told about the risk of a particular injury. A subject need not understand the content of a consent form nor be provided a reasonable opportunity to ask questions about a project in order to give legally effective consent. Documentation is the major reason why there is little successful litigation against physicians doing research compared to their colleagues practicing routine medicine.[55]

Even if a consent form provides sufficient information explained with such appropriate vocabulary that it permits understanding by subjects of all pertinent aspects of a research project, it does not guarantee voluntary consent. History has demonstrated that investigators, although trustworthy in general, are only "as humane as other men. Protection of the autonomy and voluntariness of subjects has appeared to require extensive regulations and review committees. However, no matter what number of "vexatious restrictions" are placed upon researchers, the privacy of the physician- patient and the investigator-subject relationships will always permit a certain freedom

in the negotiation of consent and especially in the protection of voluntariness.

Besides specific restrictions on research with prisoners, children and the mentally ill, the following, broadly worded statements are the extent to which regulations intervene to protect the voluntariness of subjects' decisions to consent to participation in research:

> *... An investigator shall seek [legally effective, informed] consent only under circumstances that provide the prospective subject ...sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.*[56]

> *... Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically disadvantaged, [IRB approval requires that] appropriate safeguards have been included in the study to protect the rights and welfare of these subjects.*[57]

Physician-Patient and Investigator-Subject Relationships

Rule I of the Nuremberg Code suggests a contractual relationship between researchers and subjects:[58]

> *The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.*

In medical practice, the consenting process consummates the implicit contractual relationship between physicians and patients. When a consent form is signed - as when patients-subjects decide to undergo a procedure and to participate in research - this contractual relationship becomes explicit. In business transactions, the contract is commercial in nature. Each party is responsible for obtaining information about the contract and understanding its terms and implications. Businessmen are profit-motivated, self-motivated and not expected to take measures to protect the personal freedom of their clients. In medicine, the contract is fiduciary in nature. Physicians and other professionals (e.g., lawyers, clergymen) who provide expert services because of special training, experience and institutionally validated status,[59] *must assume a more specific standard of respect for persons (clients). Their fiduciary relationship with patients-subjects requires greater respect for autonomy and therefore a greater duty to observe the conditions of valid, informed consent. Both commercial and fiduciary contracts (the latter being embodied in consent forms) are legal proof*

of consent. The difference is their respective purposes: a tool to document explicit liabilities versus a guide to promote respect for persons.

Beecher postulates that a benevolent investigator assures greater protection of subjects than does informed consent:[60]

> *An even greater safeguard for the patient than consent is the presence of an informed, able, conscientious, compassionate, responsible investigator, for it is recognized that patients can, when imperfectly informed, be induced to agree, unwisely, to many things...*

Expressing comparable idealism, Katz imagines that informed consent should unite the investigator and the subject in a partnership:[61]

> *... Informed consent would entail, if it is truly seen as an invitation, asking for consent, seeking authorization to proceed, and not making a demand under the guise of a symbolic egalitarian gesture. It would necessitate sharing knowledge and admitting ignorance, answering questions and identifying unanswerable questions, appreciating doubts and respecting fears... It requires that the interaction between investigator and subject become a partnership, giving the subject the right to determine what should be done for and with him, and forcing the investigator to be explicit in what he wants to do and why.*

The fiduciary relationship helps to equalize the imbalance of power between physicians and patients. The status of being a patient implies dependency, passivity and diminished freedom to make choices. The sick person is emotionally, personally committed to the physician's explanations about diagnosis and prognosis and recommendations about

treatment. The sick role, in proportion to the severity of the illness, embodies an exemption from normal, social duties and responsibilities (e.g., from continuing with employment or from making decisions); to be legitimized, however, this exemption requires that the sick person "be taken care of:" that he seek the help of and cooperate with a physician.[62]

In the purely therapeutic setting, this status can justify paternalistic acts aimed at benefiting patients who are believed to be incapable of acting rationally on their own behalf. Therapeutic privilege justifies a physician in limiting the disclosure of information about risks of procedures when the disclosure would seriously upset a patient and therefore be medically contraindicated. Unfortunately, therapeutic privilege also accomodates abuse of the faith patients have in physicians. Patients who can act rationally should be encouraged to do so. Instead of promoting paternalism, the fiduciary relationship is intended to promote self-determination through informed consent and to restrain physicians from imposing unwarranted paternalism upon autonomous persons.

Some freedom is permitted between physicians and patients that should not exist when the physicians are also investigators. Because the purpose of research is to develop generalizable knowledge and to benefit society and because the procedures in research are tried with uncertain results and possible risks, subjects should be protected against the potential for exploitation. In accordance with the elements

of informed consent in medical practice, investigators must, with rare exception (e.g., an emergency), fully inform potential subjects and then assess their comprehension and voluntariness. In the name of patient welfare, paternalistic acts should not justify exploitation of patients' dependency on physicians and violation of subjects' rights to be informed, weigh harms and benefits, consider alternatives and ask questions. For example, a researcher should not avoid informing a patient (subject) about the alternatives to treatment available in an investigational protocol because he thinks they will only confuse and upset the patient.

Freedom of choice is most threatened when physicians take advantage of their power because they believe they are acting for the benefit of patients. Therapeutic privilege has absolutely no relevance in protocols that are not combined with therapeutic benefit.[63] *It has limited relevance in innovative practices when disclosure of information might upset a patient so much that the patient no longer can evaluate objectively the risks of a diagnostic procedure or treatment. Whereas patients in a purely therapautic setting are entitled to delegate decision-making authority to their physicians, they relinquish this entitlement when they become research subjects. If the research incorporates no therapeutic components, investigators should treat patients as they would treat healthy, normal volunteers: obtain valid informed consent or forego the research. Patients' right to delegate authority and to refuse information about a procedure diminishes as the*

procedure involves fewer therapeutic benefits and is conducted more in the interests of research than of standard practice.

When the roles of clinical practitioner and investigator overlap, conflicts of interest can impair patient care. The role of a practitioner may be compromised by concerns about diagnostic, revenue-producing tests and payment for services. These concerns, however, do not inherently conflict with the objective of due care of individual patients. The role of a research scientist is guided by pressures to generate high quality data and to test hypotheses. Financial rewards through grants and contracts, academic advancements and reputation, obsessive scientific interest - all these personal objectives may directly subtract from the objective of patient care and may add to pressures upon investigators to use subjects as means to ends only. Although both roles are justified by benefiting the sick, the practitioner benefits patients immediately while the investigator provides potential benefits to future patients.

Even in protocols that offer extremely large, potential benefits to society, compromise of patient care violates the principle of beneficence and is not justified. Physicians entrusted with the care of patients should not use their status to obtain a signed consent form rather than to seek voluntary, informed consent. Patients with minor disease would rather give consent to participation in research conducted by their physician than take a chance of jeopardizing their future relationship when seriously ill. Dying persons and persons with a

prolonged or painful chronic illness are particularly vulnerable to invitations to participate in research. For example, patients with end-stage cancer who have exhausted standard treatments usually do not feel a sense of final duty or curiosity about trying investigational drugs. Instead, they may feel stranded without the hope of therapeutic options, in need of attention (even by research staff), desperate for a miracle cure and vulnerable to any invitation to try new chemotherapy when it is made available through a protocol. Such patients usually sign a consent form.

Other classes of persons besides hospitalized patients are vulnerable to inducements to consent to participation in research. Prisoners, students and staff of researchers, the elderly, unemployed, uneducated and impoverished - all healthy, normal persons - have particular constraints upon their freedom to make choices about refusing to participate in certain kinds of research. While patients, in general, enlist in protocols that offer some therapeutic advantages, other vulnerable persons are invited to consent to research procedures that frequently do not benefit them directly. These other classes of potential subjects are lured by monetary inducements.

VULNERABLE PERSONS

The gross abuses against voluntariness in Nazi prisoner camps provide rare examples of coercion in (what was claimed to be) biomedical research. The Nuremberg Code and subsequent federal regulations on informed consent and IRB review were formulated to ensure that these gross abuses never reoccur. And they have not. Therefore, because regulations have prevented what are obviously unjustified interventions between investigators-subjects, emphasis has turned towards refinements of what are less clearly unjustified interferences with freedom of choice.

Rule I of the Nuremberg Code states that subjects be "so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress or any other form of constraint or coercion." In other words, persons must be free to refuse participation in research. In the vast pool of society's potential research subjects, most persons do not need special protection of autonomy in the consent process. Some persons, however, are vulnerable to inducements to participate in research. Levine defines vulnerable persons as "those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they have insufficient power, prowess, intelligence, resources, strength or other needed attributes to protect their own interests through negotiations for informed consent."[64]

The extent to which persons are vulnerable, like the range of interventions in freedom of choice (from coercion to persuasion), establishes a continuum. For example, all persons are tempted by offers of large sums of money. But compared to relatively affluent individuals who may desire to become more wealthy, impoverished individuals "consider it necessary to assume extraordinary risk or inconvenience in order to secure money or other economic benefits that will enable them to purchase what they consider to be the necessities of life."[65] *Compared to wealthy persons, impoverished ones are more likely to participate because of monetary inducement.*

Prisoners and Vulnerability to Monetary Inducements

Prisoners exemplify a population of healthy, nonhospitalized, potential subjects who are vulnerable to inducements to participate in research. In 1968, Martin and his colleagues studied the likelihood of securing research subjects from different classes of persons.[66] *They considered four different protocols presenting a range of risk and discomfort. They found that all classes of persons were likely to volunteer for the protocol presenting the least risk and discomfort. As the risk increased, however, prisoners were most likely to volunteer, followed by fire and police personnel and, finally, professionals.*

Although recent legislation has substantially curtailed research conducted in prisons, this discussion assumes that prisoners, under the appropriate circumstances, should be allowed to volunteer as research

subjects. According to the principle of respect for persons, prisoners should not be deprived of the opportunity to make decisions about their lives. Any systematic deprivation of this opportunity would violate the principle of justice (the fair distribution of burdens and benefits) by arbitrarily excluding prisoners from access to the benefits of participation in research.[67] *Both the principles of respect for persons and beneficence imply that the liberty of persons, because incarceration removes so many options, should not be reduced further by removing yet another option: participation in research.*[68] *These principles also require, however, that prisoners be protected from exploitation. Given that prisoners have a right to participate in research, this protection should involve maximizing voluntariness by minimizing vulnerability and constraints on self-determination.*

The prison environment is designed to foster submission, conformity, and "to surround the inmate with symbols of constraint, isolation and intimidation; these include the massive gates, thick walls, and armed guards."[69] *To effect criminal punishment and rehabilitation, the prison environment establishes a deliberate dependency on authority. Prisoners are not supposed to make decisions or to control their conditions of confinement. Constant supervision and inspection place intrinsic constraints on their freedom and privacy. These conditions are unavoidable. Avoidable conditions exist, however, and include substandard living conditions such as inadequate medical care, lack of basic amenities for personal hygiene, overcrowding and limited opportunity to fulfill a need to work.*[70]

Prisoners are deprived relative to the rest of society and therefore have less to lose and more to gain by participation in biomedical research. Institutionalization creates deprivation, drabness and boredom; prison life dictates monotonous routine from which any change can bring relief. Incarceration, even if work is available, prevents substantial monetary reward. Most prisoners are impoverished - states usually pay the incarcerated less than one dollar per day[72] - and seek any alternative means to earn money. Parole and reduction of sentence dominate prisoners' concerns. Prisoners are desparate to demonstrate any "good behavior" that they perceive will influence positively the parole board and prison officials.[73] Participation in research offers "...an opportunity to prove one's good will, one's eagerness to pay his debt to society, one's sincere intention to make up for past evils and be good!!"[74]

Wells and his colleagues in 1975 published the results of a study of prisoners' motivation to participate in research.[75] Prisoners' reasons were ranked in this order: 1) opportunity to make worthwhile contributions to benefit society, 2) opportunity to make worthwhile contributions to benefit medical science, 3) curiosity, 4) opportunity to improve living conditions, 5) opportunity to exhibit courage, 6) need for money, 7) opportunity to relieve the boredom of prison life, 8) opportunity to receive better treatment from officers and other correctional staff, 9) opportunity to be part of a group and meet others, 10) greater chance of getting a job or position upon release,

11) opportunity to stay out of trouble, 12) opportunity to take drugs, 13) greater chance of getting an earlier parole, 14) opportunity to be excused from doing other activities, 15) a close friend was already participating, 16) opportunity to escape from feared others, 17) opportunity to receive better health care, 18) opportunity to feel more important, 19) reduction of present and/or future restrictions and 20) opportunity to be admired by other prisoners.

Except for the hope of an earlier parole, these reasons are similar to those ranked by "normal," nonprisoner volunteers. Altruism and curiosity are principal motivations. Both are ethically acceptable. Although other incentives such as earlier parole might be more important to prisoners over the long term, cash payment for participation in research provides such a rare opportunity to make money that one would think it should rank higher on the list. In fact, in spite of Wells' results, most scholars still maintain that valid, informed consent is vitiated "by forces ...that unduly influence,"[76] - as by cash payments.[77]

Until regulations in 1981 resulted in a moratorium on research in prisons, most research involving prisoners was funded by private pharmaceutical companies conducting phase I drug studies of metabolism and bioavailability. In fact, almost all phase I studies were done on prisoners.[78] While investigators and society at large derived important pharmacological information and improvements in medical care from these trials, prisoners as a class were rarely full beneficiaries

of the improvements in medical diagnosis and therapy. Because payment was the primary benefit in participation in phase I trials, prisoners provide a model of persons vulnerable to cash payments.

Cash payments made by drug companies to nonprisoners are both customary and ethically acceptable.[79] However, when prisoners are invited to consent to participation in research, monetary inducements introduce complex and conflicting ethical issues. For example, some drug companies pay wages fifteen times greater than those paid in other prison jobs.[80] Because these wages are still one tenth the amount paid to nonprisoners, there is conflict between a monetary reward that is so small as to violate equal treatment of persons (the fair sharing of the benefits of participation in research) required by the principle of justice but so large as to violate freedom of choice required by the principle of respect for persons. This conflict introduces several of the obstacles in deciding what is excessive, or undue, payment. In the following chapter, these obstacles willbe examined in detail.

Justice: Prisoners should be treated fairly and should be paid wages equal to what nonprisoners are paid for participating in the same research - no more and no less. A discussion of the validity of this statement introduces the dilemma of opposing precepts of justice and the conflict between protection of vulnerable persons and equal pay for equal work.

If prisoners are paid less than nonprisoners, they are denied benefits that nonprisoners receive for participation in the same research. This disparity may not be unfair, however, because only equals should be treated equally. Unequals should be treated unequally when the differences are ethically relevant. In the case of prisoners, incarceration and inability to earn money may result in a substantial vulnerability to payment compared to nonprisoners. When this difference in vulnerability becomes ethically relevant, the principle of respect for persons conflicts and prevails over the precept of justice requiring equal pay for equal work. This vulnerability should be minimized by paying less money to prisoners than to nonprisoners.

The less that prisoners are paid for participation in research, however, the more that drug companies have an economic incentive to concentrate their drug testing in prisons. Prisoners not only receive fewer of the monetary benefits of participation in research compared to the rest of society, they become means to others' financial ends. In addition, since subjects' wages are small compared to the overall cost of drug approval, the economic incentive may not be most important. Drug companies also employ prisoners as research subjects because of convenience and expediency.

No class of persons is better suited than a prison population for phase I trials requiring long-term regularity and control of subjects' conditions.[81] *Prisoners live in environmental uniformity and constitute a stable, confined population ideal for the monitoring of*

diet, activity and other research parameters. From the point of view of drug companies' investigators, prison populations can conveniently devote time to lengthy, repeated trials and can optimally serve medicine and scientific efficiency.

If prisoners are paid less than nonprisoners, the principle of respect for persons also conflicts with a second precept of justice requiring fair distribution of research burdens. Whether the incentives to drug companies are economic or utilitarian, concentration or phase I trials in prisons causes inmates to assume a larger share of the burdens of participation in research. In its deliberations on research involving prisoners, the Commission considered it important "...to ensure the equitable distribution of the burdens of research no matter how large or small those burdens of research may be."[82] *The Commission recommended that research in prisons should be limited to: "[s]tudies of the possible causes, effects, and processes of incarceration and studies of prisons as institutional structures or of prisoners as incarcerated persons ... provided that they present minimal or no risk and no more than mere inconvenience to the subjects."*[83] *In addition, it permitted "[r]esearch on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the individual prisoner..."*[84]

Respect for Persons: Prisoners should be provided maximum freedom to refuse participation in research and should be paid sums commensurate with payments in other prison jobs - no more and no less.

A discussion of the validity of this precept of respect for persons introduces the problem of paternalism and the concept of risk.

In the deprived prison environment, a payment fifteen times greater than in other job opportunities may impair the rational capacity of prisoners in at least three ways. First, this payment may cause prisoners to enter a research project when they would be unwilling to do so if the payment was reasonable (i.e., in proportion to other prison wages) or if they were not incarcerated. Second, it may cause them to give insufficient consideration to the risk of bodily injury (if the protocol presents any risk). Finally, it may cause prisoners, once they are entered into a protocol, to continue as research subjects and to remain quiet about adverse reactions that would cause the displeasure of prison authorities and their dismissal from the protocol.[85]

Although impoverishment may cause prisoners to expose themselves to greater risk in order to secure a tempting sum of money, it does not follow that impoverishment necessarily is ethically relevant and impairs their capacity to make rational decisions. Cohen, a philosopher at the University of Michigan, has affirmed the rational capacity of prisoners: "If the standard of [voluntariness] be that potential subjects be free of all conditions that may significantly influence their willingness to consent, we will have no subjects and no research."[86] *Like other persons, prisoners make decisions that are influenced by the constraints of their particular situation. Constraints such as poverty and low paying jobs give prisoners good reasons to seek alternatives for earning*

money and not to refuse participation in research. Unless these constraints diminish prisoners' autonomy in a way that is determined to be ethically relevant, they do not justify protecting prisoners by restricting payment. Protection of autonomous persons constitutes unwarranted paternalism.

Furthermore, if a tempting sum of money does impair prisoners' rational capacity, it does not follow that temptation necessarily is ethically relevant and violates the principle of respect for persons. As shall be discussed, diminished autonomy and a tempting sum of money are by themselves insufficient criteria for identifying excessive payment. The third criterion is the degree of risk presented by the research. There is no ethical relevance if the research presents little potential for harm. If a tempting sum of money is offered in return for participation in research that presents little risk, the mere fact that prisoners' situation makes the reward exceptionally attractive does not necessarily mean that undue inducement has been applied.[87] *On the other hand, if the research presents significant risk of injury, a tempting sum of money violates the principle of respect for persons and justifies restricting payment so that prisons deliberate more seriously about their best interests.*

Although phase I drug trials always present a risk of unknown injury from the investigational drug's side effects, they almost always do not result in this injury. If there is no need for prisoners to be able to protect themselves from bodily harm by weighing the harms of

participating against the benefits, then there is no entitlement to protection from harm by restrictions on payment. In general, the fewer the potential harms presented by research, the larger the permissible inducement.

In its deliberations on research involving prisoners, the Commission suggested various solutions to the problem of cash payment:[88]

> *... Fair solutions to this problem are difficult to achieve. One suggestion is that those who sponsor research pay the same rate for prisoners as they pay other volunteers, but that the amount actually going to the research subject be comparable to the rates of pay otherwise available within the facility. The difference between the two amounts could be paid into a general fund, either to subsidize the wages for all inmates within the prison, or for other purposes that benefit the prisoners and their families. Prisoners should participate in managing such a fund and in determining allocation of the monies. Another suggestion is that the difference be held in escrow and paid to each participant at the time of release or, alternatively, that it be paid directly to the prisoner's family.*

The extraordinary constraints of incarceration complicate an analysis of what is excessive, or undue, monetary inducement Poverty is not an isolatable factor in prisoners' vulnerability to participation in research. Focusing on impoverished classes of persons better illustrates vulnerability to cash payments and provides the basis for distinguishing between due and undue inducements.

DUE AND UNDUE MONETARY INDUCEMENTS

Three factors can be immediately identified as potential critieria for defining and distinguishing between due and undue monetary inducements to participate in research. These factors are impoverishment of subjects, the size of payment and the risk of injury in participation in the research. They will provide the framework for a systematic analysis of due and undue monetary inducements. In order to narrow the scope of this analysis, it is stipulated that:

1) the subjects are normal, healthy persons.
2) the subjects comprehend fully-disclosed information; only their voluntariness is in question.
3) the subjects participate in research that confers no direct, health-related benefit.
4) the investigators do not offer money to manipulate deliberately subjects' impoverishment. Investigators are simply reimbursing subjects for their time and energy in order to obtain a sufficient number of research subjects.

Within these boundaries, impoverishment of subjects and size of payment will be explored in two research protocols. One protocol involves minimal risk of injury to subjects while the other involves significant risk. Before continuing with these protocols, however, certain concepts should be clarified.

Normal, Healthy Persons: Instead of patients who are sick or dying and persons who are institutionalized, potential subjects in this discussion are limited to classes of normal, healthy persons. These classes of persons can be distinguished by financial need and can be

separated into three groups. This separation is grounded in an objective appraisal of the intrinsic need of money by persons in each class. The most financially deprived classes of persons are included in one group: the unemployed welfare recipients and the elderly surviving on Social Security. They usually do little to consume their daytime hours and lack the usual means of earning enough money to purchase basic necessities. The most financially independent classes of persons are included in another group: professionals such as corporate executives and lawyers who, without exception, would make more money at the office than at the clinical research center (CRC). They have little extra time to devote to activities outside of their career. The last group includes classes of persons with an intermediate degree of need of money: the large pool of students in undergraduate and medical colleges who enroll routinely as subjects in research protocols to make money on short notice and with brief time commitment.

Voluntariness: Assuming that potential subjects understand information that is fully disclosed, the only obstacle to valid, informed consent is their voluntariness. The effects of cash payments on voluntariness can be broken down into problems presented by intrinsic and exrinsic constraints.

One problem in defining a single monetary sum as due or undue is that each group has different intrinsic, financial needs. An objective assessment of the relative impoverishment of potential subjects is grounded in the determination of employment status, educational status

or status of family and financial dependents at home. This information is obtained in every complete history. An adequate assessment does not require knowing exactly the amount of income earned or tuition paid. The important point is that a dollar has more value for persons with low income than for those who are rich; moreover, all other factors (e.g., extrinsic constraints) being equal, relative income reliably predicts when a sum of money is an unrefusable offer and when it is a slight temptation.[89] *Considering only intrinsic constraints, this prediction is accomplished simply by ranking subjects' need of money. This need is proportional to vulnerability to cash payments. After a complete history, investigators should be able to identify classes of impoverished persons (if these persons do not lie) and, therefore, to begin the determination of an appropriate material reward.*

Another, more complex problem in defining objective criteria for distinguishing between due and undue inducements is that individuals attach different values to money.[90] *They have different extrinsic constraints on voluntariness depending on their work ethic, sociocultural context and personal idiosyncrasies. For example, some persons who sell investment bonds on a commission basis are willing to work fourteen hours a day in exchange for substantial additional income. Others place greater value on leisure time or family life and prefer to work the minimum hours necessary to earn a salary that supports their life style. Thus, within a group, some subjects perceive a particular cash inducement as irresistible while others who earn the same amount of money perceive that payment as unremarkable.*

There are no objective measures for ranking individual, subjective perceptions of the importance of money. Pragmatically, investigators cannot assess the value schemes of potential subjects. It would require greater communication between investigator and subject than even Katz envisions in his ideal partnership; more than "...sharing knowledge and admitting ignorance, answering questions and identifying unanswerable questions, appreciating doubts and respecting fears,..." it would necessitate a complete psychosocial evaluation. According to Macklin, who is Associate Professor of Community Health at Albert Einstein Medical College, the different value schemes among persons "present almost insurmountable difficulties for any attempt to find a workable criterion for distinguishing due from undue monetary inducements to serve as a research subject." On this point, Newton, who is professor of philosophy at Fairfield University, concurs that "...to provide equal 'inducement' to different people would require offering a different amount of money to each person for the same work." It is the effect of the payment, not its size,that determines undueness.

Cash Payments: Payment of research subjects would be unnecessary if enough persons volunteered because of curiosity or altruism. Cash payments have become traditional and customary, however, because without sufficient compensation, inadequate numbers of subjects would consent to participate in today's numerous Phase I drug trials and protocols investigating normal physiology. Although the scientific and medical knowledge gained through these research projects provide

important health-related benefits to society as a whole, none of these benefits are offered directly to the subjects. Instead of medical benefits, these normal, healthy volunteers decide to participate in research because of monetary benefits. The greater the cash payment, the more seriously potential subjects consider consenting to participate.

Concept of Risk: Equal in importance to the vulnerability of potential subjects and the size of cash payments, the risk involved in a research project is a factor in distinguishing due from undue monetary inducements.

The term "risk" entails a prediction of some future occurrence of harm.[91] In general, the risk of physical or psychological harm to normal, healthy research subjects is not especially significant; being a research subject is usually not hazardous.[92] One study has demonstrated that the risks to subjects in Phase I drug trials are somewhat greater than those of being an office secretary, one-seventh those of window washers and one-ninth those of miners.[93] Another study surveyed Phase I drug trials in prisons and determined that a "clinically significant medical event" occurred once every 26.3 years of individual subject exposure.[94] In 805 protocols involving 29,162 prisoners over 614,534 days, none of the 58 adverse drug reactions caused death or permenant disability (one of these prisoners died while receiving a placebo).

According to DHHS regulations enacted in 1981, "'minimal risk' means that the risks of harm anticipated in the proposed research are not greater considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (Section 46.102). Minimal risk excludes the slightest possibility of physical or psychological injury. It describes burdens imposed upon the research subject that are more appropriately referred to as inconvenience, embarrassment and discomfort. Thus, because minimal risk implies only the slightest risk, more accurate terminology may be "mere inconvenience."[95] *For example, research procedures that present minimal risk (mere inconvenience) include being observed in a clinical research center, answering a questionnaire, having blood drawn and collecting urine or feces.*

Research maneuvers presenting more than minimal risk to normal, healthy volunteers need appropriate justification. In research involving patients, diagnostic and therapeutic maneuvers (nonvalidated practices) may present substantial risk of physical and psychological injury but still may be justified by the expectation of benefit for individual patients as well as for society as a whole.[96] *In research intended to contribute only to generalizable knowledge, the only justification of risk to normal, healthy volunteers is the potential benefit to society. Because these volunteers derive no health-related benefits, the Commission cautioned against exposing them to "unreasonable risks." It did not recommend, however, that IRBs should become paternalistic guardians. The Commission emphasized subjects'*

responsibility to weigh for themselves the risks of research against its advantages:[97]

> *... [I]f the prospective subjects are normal adults, the primary responsibility of the IRB should be to assure that sufficient information will be disclosed in the informed consent process, provided the research does not present an extreme case of unreasonable risks.*

Just as individuals attach different weights to money, so they attach different weights to risk and to the advantages and disadvantages of participating in research. What some persons perceive as dangerous research because of potential risk of injury and discomfort, other persons treat indifferently and gladly accept to gain significant remuneration. This willingness or unwillingness of subjects to expose themselves to risk and discomfort further complicates an evaluation of the dueness of cash payments. If there is no standard measure of unreasonable risk, there is no standard measure of undue inducement. Ideally, persons who place high value on money and low thresholds on risk should be treated differently from those who place low value on money and high thresholds on risk.

Research Involving Minimal Risk

Consider a phase I drug trial in which the investigational drug is administered by intravenous infusion. The protocol requires an overnight stay in a clinical research center, timed collections of blood and urine, measurements of vital signs and questionnaires about side effects. Although the probability and magnitude of harm from this particular investigational drug is unpredictable in humans, phase I trials in general (based on review of millions of days of exposure of normal subjects to phase I drugs) present minimal risk. Other "risks" of participation include the probability of inconvenience or embarrassment because of bruising from intravenous catheters, urinating into a plastic jug, sleeping in an unfamiliar setting and being awakened throughout the night. Recruitment is accomplished by flyers posted on bulletin boards in churches, unemployment offices and university corridors and dormitories. Subjects are fully informed. Written consent is documented. Subjects are paid the hourly, minimum wage.

As shall be shown, minimum wage does not predominate over the will of normal, healthy students, professionals or impoverished persons. It does not impair their capacity to weigh the possible inconveniences presented in this drug trial. Therefore, minimum wage does not violate the principle of respect for persons and is not an undue inducement.

Students: Students generally have a number of work options available to them. Since they are able to join work-study programs or

find other jobs that pay minimum wage or more, the inducement to consent to participation in this drug trial cannot be undue. It does not predominate over students' will. In fact, minimum wage may be too low for students to consider it seriously as a due inducement. If their goal is to earn money, students often elect to expose themselves to greater discomfort by working longer, more pressured hours in a restaurant or bar.

An undue payment impairs potential subjects' capacity to judge the risk of participation in research. This impairment is not ethically relevant if the research presents little risk of injury. Although an investigational drug presents a possibility of harm due to unknown reactions and side effects, such reactions are rare in phase I trials. (The inconveniences in this study are minimized further if the subjects are medical students or graduate students at a medical center; there is not the usual anxiety and nausea at the sight of intravenous catheters, at the thought of infusions of chemicals and not the usual embarrassment over urination into plastic jugs.) Because subjects do not need to be able to protect themselves, the loss of their capacity to judge risk is a moot issue. Because there is little risk in participation, subjects do not need protection from harm by restrictions on payment.

Participation in this study can be regarded as regular employment. There is no difference between payment to participate in this study and payment to do unskilled labor. Students render a service to investigators: cooperation; in return, investigators compensate students

for their time and inconvenience. Because students are compensated only for time and inconvenience, they are not different from other unskilled employees (e.g., janitors and nighttime security guards). Just as market forces determine the wages earned by unskilled laborers, so these market forces should determine the wages earned by students in phase I drug trials.

Just as the participant in this phase I drug trial is an employee, so the investigator is an employer. The contractual relationship between investigators and subjects becomes more commercial than fiduciary. As long as the recruitment techniques are fair (e.g., students are not pressured to participate because they are members of the primary investigator's laboratory staff), the subjects' status is in no way passive or dependent. The students do not require the expertise of physicians to understand the risk in participation. There are no procedural details or implications that cannot be completely elucidated in a consent form. In contrast to the relationship between patients and physicians, this relationship between students and physicians implies no passive, emotional subjugation. There is no need for subjects to put faith in the expertise and skills of investigators. There is no special trust or covenant. The fiduciary relationship loses its relevance.

As employers, investigators advertise their job opportunity by posting flyers in those areas frequented by prospective candidates. After recruiting applicants, investigators interview them to assess their qualifications for the job (i.e., good health that is

uncomplicated by major medical problems that might interfere with an accurate determination of the investigational drug's bioavailability, metabolism and excretion). After applicants are informed of the conditions of employment (including salary), they sign a contract (consent form) if they want to be hired.

A common instance in which investigators act as employers includes research involving questionnaires. Consider research in which students answer questions, for example, about attitudes towards parental discipline. In addition to the usual safeguards ensuring confidentiality, students do not have to answer any questions that they do not want to answer. The only inconveniences are time commitment and, however unlikely, psychological stress related to memories about heavy-handed parental discipline. Because subjects are not dependent for their safety upon the expertise of the investigators as physicians, there is no imbalance of power between subjects and investigators. There is no possibility of undue inducement. Although prudent investigators will want to keep the levels of pay low, no amount of money would be too much.

Referring again to the phase I drug trial, if instead of minimum wage the payment is one or two dollars hourly, students would not seriously consider wasting their time at a clinical research center. As noted already, they have access to many job opportunities that pay minimum wage or more.

Consider an equally unrealistic wage of fifty dollars per hour. There is nothing about phase I testing that suggests that subjects deserve greater payment than the hourly minimum wage. There are no harms or discomforts for which there should be extra reimbursement. Participation in research as a noble pursuit and for the sake of mankind does not in itself merit extra reward. If for some reason, however, the wage does happen to be as substantial as fifty dollars per hour, does so much money violate the principle of respect for persons? This salary would probably cause students to ignore the risk of injury in phase I drug testing. Because this risk is minimal, however, the incapacity of vulnerable persons to refuse participation is irrelevant. Students, however diminished their autonomy because of need for money, are not treated as means to ends by an inflated payment to participate in phase I drug testing any more than they are by the same payment to sweep hallways. For the fortunate students who happen to come across the flyers advertising this research, the bigger the inducement the better.

Furthermore, fifty dollars hourly wage does not violate the principle of justice. Since this phase I study presents practically no risk of injury, there can be no disproportioning of the burdens of serving as research subjects. If the risk is not ethically relevant, unwarranted paternalism occurs when the principle of justice is applied to justify protection of impoverished persons. Students who participate as subjects probably assume fewer burdens than if they decided to work in a restaurant or bar.

A payment as large as fifty dollars per hour can become an undue inducement, however, if subjects are not normal, healthy volunteers. Macklin has stated that: "Inducements are undue if they prompt subjects to lie, deceive, or conceal information that, if known, would disqualify them as participants in a research project."[98] *Thus, if the investigational drug has been shown to be hepatotoxic in animals with underlying liver disease, investigators would include as part of their exclusion criteria a history, for example, of viral hepatitis. A subject who lied about a history of jaundice secondary to hepatitis B infection would be exposed to a greater risk of injury. Since the decision to lie and to ignore this risk of injury both result from subjects' perceived need of money, the payment predominates over the will of the subject and is undue. Although such a drug trial presents no greater risk to normal, healthy subjects than does the one previously described, the subject in this example has lied about a significant medical problem. The more an individual differs from the ideal of a normal, healthy volunteer, the less he or she falls within the boundaries of this discussion.*

Impoverished Persons: In this phase I drug trial as well as in other research involving only time and inconvenience, the same considerations apply to the working poor and to unemployed welfare recipients as applied to students (incidentally, students sometimes have less money than either of these classes). If participation exposes subjects to minimal risk of injury, compensation should be unrestricted.

Because there is no concern for undue monetary inducement, market forces should determine the wages earned by financially deprived persons.

Although large payment is ethically justified, small payment raises the question of fair sharing of research burdens in society and violation of the principle of justice. In accordance with the forces of supply and demand, investigators would offer the lowest wage that could attract sufficient numbers of research subjects. If payment falls below minimum wage, recruited subjects would probably be in the lower social and economic classes. Despite this selection bias towards impoverished persons, however, there would be no violation of the principle of justice in phase I testing. The risk of injury, although finite, is too small to be ethically relevant to considerations of equitable distribution of research burdens in society.

If justice required equal sharing of research burdens "...no matter how large or how small those burdens may be", protection of subjects would require raising the payment until a sufficient number of higher wage earners decided to participate. Pragmatically, the Commission's concerns are untenable. This protection would be ineffective: unless payment is increased substantially above what volunteers are paid customarily, there is little incentive for higher wage earners to participate.

Professional Classes: For professionals, as for students and impoverished persons, no inducement is undue for participation in phase

I drug trials. Most likely, no payment could surpass the earning potential of professionals who stayed at work in the office. In addition, professionals are unlikely to learn about a drug study. Since recruitment is conducted among those populations expected to become volunteers, professionals rarely see flyers advertising the research.

Research Involving More Than Minimal Risk

Consider a study of physiological mechanisms in the regulation of hepatic glucose uptake in normal, healthy subjects.[99] *Following an overnight fast, the procedure involves insertion of three short catheters and one long one. One short catheter is inserted into a peripheral arm vein for infusion of substances; another into a femoral or brachial artery for taking blood samples; and the third into a femoral vein for sampling blood from the leg. The long catheter is passed, under fluoroscopic control, via a peripheral arm vein, through the right atrium and into the hepatic vein (if there are no suitable arm veins, a femoral vein is used). After the catheters are placed, a dye is infused (to measure hepatic blood flow) for one hour followed by infusion for another hour of either saline, propranolol, phentolamine, or both propranolol and phentolamine. A 200 gram glucose load is ingested followed by an additional four hours of infusions. Over the six hour study, approximately 300 ml of blood is drawn. Risks include: subcutaneous hematomas, venous or arterial thrombophlebitis, venous perforation by the long catheter, arrhythmias, hypotension secondary to propranolol or phentolamine, and low-dose radiation exposure.*

This discussion of research involving more than minimal risk focuses upon impoverished persons who, given their economic deprivation, comprise the population most vulnerable to monetary inducements. If unrestricted payment of impoverished persons could be justified for participation in research involving risk of injury, then, everything

else being equal, unrestricted payment of students and professionals, who have more opportunities to earn money, would also be justified.

In this study of normal physiology, minimum wage is not undue inducement for impoverished persons. Before developing reasoning why minimum wage doe not violate the principle of respect for persons, it is instructive to clarify certain distinctions between research involving minimal and higher risk. Relevant distinctions occur in purpose of payment, violation of justice, and job status.

Payment: In both protocols, payment has two purposes. In addition to remuneration for the services rendered by subjects, payment acts as an incentive, or temptation, "...without which too few subjects could be recruited."[100] *Remuneration to subjects - what is their due for participation in research - embodies the notion of what is a fair, or just, wage. Incentive to subjects, on the other hand, is determined solely by supply and demand. In the phase I drug trial, there is no distinction between payment which is a fair salary for subjects' time and energy and that which is an incentive dependent on market forces. In the physiology protocol involving invasive procedures, however, increased payment remunerates not only for subjects' time and energy, but also for their exposure to extra risk of injury and the likelihood of pain. Because of greater risk of injury, payment which is fair salary can surpass that which merely induces the participation of sufficient numbers of subjects. If the payment to subjects in this portocol is minimum wage, for example, impoverished persons are not*

offered fair remuneration for their exposure to possible inguinal hematoma, groin pain and femoral venous thrombosis.

As discussed shortly, a wage that fairly remunerates research subjects may violate the principle of respect for persons by causing undue inducement, particularly in the case of impoverished persons, to participate in research presenting risk of injury. As discussed first, however, a low wage that merely attracts a sufficient number of subjects may violate the principle of justice.

Justice: When research presents risk of injury, market forces can create a selection bias towards impoverished persons who not only earn a disproportionately low wage (e.g., compared to football players or divers who also place themselves at risk of injury), but also bear a disproportionately large share of research burdens in society. In general, as the probability and magnitude of injury increase, a significant difference can occur between the amount of money required to remunerate for exposure to risk and that required to induce the participation of a sufficient number of persons most vulnerable to offers of money. In deciding on the payment of subjects, investigators, to save money, may be disposed to offer an amount commensurate with an incentive instead of due remuneration. They would set payment low initially, raising it gradually until enough subjects had been recruited.[101] *In an attempt to justify this reimbursement scheme, investigators might argue that just as market forces determine what payment shall be made to subjects participating in research involving*

only time and inconvenience, so these forces should determine payment in research involving risks.

When research procedures involve sufficient risk of injury, reliance on market forces can result in disproportionate sharing of research burdens. As Macklin states, "[s]etting the payment as low as would be necessary to gain a subject pool would virtually ensure that those subjects would be drawn from lower social and economic classes."[102] *This bias is not ethically relevant in the phase I drug trial, as discussed, because the research burdens are minimal. In the physiology study, however, if payment were minimum wage, not only would impoverished persons receive payment that is low considering the risk involved, but also they would bear significant burdens that are not born by other members of society. The socioeconomic status of impoverished persons already makes them last to receive the benefits accrued as a result of the research. Therefore, the smaller the payment in this physiology protocol, the greater the selection bias towards impoverished persons and the greater the violation of the principle of justice.*

There exists a logical solution to this problem of inequitable distribution: to disregard market forces by adjusting the payment of research subjects to be in proportion to their different levels of income.[103] *This solution may create more problems than it solves, however, by conflicting with a second precept of justice that requires equal pay for equal work.*

These two precepts of justice are in such irreconcilable conflict that a choice must be made between them or the research foregone. For reasons that follow, the ethical precept requiring equal pay for equal work prevails over the one requiring equitable distribution of the burdens of research. Macklin prefers equal pay for equal work because, in the case of a variable payment scale, "[v]olunteers would be sorely tempted to lie about their income in order to receive higher pay as a research subject."[104] *There are more compelling reasons. Legally, there is no precedent for such blatant economic discrimination against disadvantaged persons (except for prisoners). Pragmatically, it would be a formidable if not impossible task to design a variable payment scale involving three or more reimbursement rates. An equally formidable task would be to determine which subjects get which rate. Although an estimate of individual income status may be obtained in a thorough history, there are, as already pointed out, insurmountable difficulties in assessing the value each person places on money and risk and the priority each places on participation in research.*

An underlying ethical objection to a variable payment scale eclipses legal and pragmatic objections. The problem is grounded in paternalism. Although a discussion of paternalism leads directly into conclusions about distinctions between due and undue inducements, it is helpful first to clarify why paternalism is commonly an issue in research involving more than minimal risk. The most important reason is exemplified by the distinction between the nature of employment in the physiology study and in the phase I drug trial.

Job Status: In the phase I drug trial, although subjects are carefully monitored by a skilled investigator, they are not usually dependent for their safety on the expertise of this investigator. "Informed consent" plays a mechanical role and the consent form only documents liabilities and responsibilities as in a commercial contract. In the physiology study, however, healthy volunteers can remain healthy volunteers only if the skills of the investigator persevere over the challenge of several venous and arterial catheterizations. Thus, subjects entrust this investigator with their health and well-being. Because a physician draws upon the same training and experience and performs the same invasive procedures in the CRC as on the hospital wards, the relationship between subjects and the investigator is fiduciary. Like a physician practicing clinical medicine, the investigator assumes a special standard of respect for persons and a special duty to negotiate valid, informed consent. Moreover, the investigator conducting this physiology study has an additional duty: to maximize the capacity of subjects to protect themselves from potential harm.

This duty to protect subjects' capacity to refuse participation in research, an ethical duty for investigators as well as a legal one for IRBs, returns the discussion to a variable payment scale and to the problem of paternalism. To be justified as a solution for inequitable distribution of research burdens, the pay scale must limit the wage of impoverished persons and must cause them to evaluate risk more carefully

and thereby to protect themselves from burdens that are great enough to be ethically relevant. Although risk may be more than minimal, the majority of protocols approved by IRBs present risk that is not ethically relevant. The physiology study, for example, presents obvious potential for causing temporary anxiety and physical discomfort, but little potential for causing severe pain and permenant disability.

In most research, therefore, whether or not every subject is an impoverished person, the risk of injury is not relevant to problems of equitable sharing of research burdens. As unwarranted paternalism, a variable pay scale violates subjects' autonomy and deprives impoverished persons of the opportunity to earn not only as much money as possible, but also as much money as students and others for participating in the same reseach. Instead of fair sharing of research burdens, the prevailing precept of justice is equal pay for equal work.

Impoverished persons' share of research burdens might be decreased more fairly by offering all subjects more money in accord with equal pay for equal work instead of selectively offering impoverished persons less money in accord with a variable payment scale. If the effect of equal pay were to raise all subjects' wages reflecting fair remuneration, fewer impoverished persons would be research subjects. Although more impoverished persons would want to earn the extra money, fewer of them would be able to participate because more students and wage earners also would want the money and would compete for the available positions. On the other hand, if the effect of equal pay were to lower all subjects'

wages reflecting market forces, impoverished persons probably would be the only subjects.

Respect for Persons: When research involves more than minimal risk, a wage that fairly remunerates research subjects may violate the principle of respect for persons. A due salary - more payment than that required to attract merely a sufficient number of research subjects - may cause undue inducement of impoverished persons to participate in research and to expose themselves to risk of injury. Although respect for persons requires treatment of individuals as autonomous agents, it also requires that individuals with diminished autonomy be protected.

Unwarranted paternalism is potentially the most important ethical objection to protection of impoverished persons. As discussed, if the risk of injury is not ethically relevant, unwarranted paternalism occurs when the principle of justice is used to justify protection of impoverished persons from a disproportionate share of research risk. Likewise, it can occur when the principle of respect for persons is used to justify their protection from payment that does not actually predominate over their capacity to refuse participation in research and to judge risk of injury. Distinctions between due and undue inducements can be approached by addressing the problem of paternalism and by contrasting the degree of need for protection of diminished autonomy between impoverished persons and other vulnerable populations.

Although impoverished persons are obviously vulnerable to monetary inducements to participate in research, they are not as constrained by this vulnerability as patients and prisoners are constrained by vulnerability to (nonmonetary) inducements. Impoverished persons are less vulnerable due to poverty than patients are vulnerable due to illness and a fiduciary relationship embodying dependency and passivity; or than prisoners are vulnerable due to incarceration and a contrived environment designed explicitly to restrict options. Therefore, self-determination is less diminished in impoverished persons than in patients and prisoners. Impoverished persons are not as entitled to protection against inducements to participate in research. Paternalism is less warranted.

Except for economic deprivation, impoverished persons are without disabling constraints (e.g., illness, incarceration, senility, and retardation) that could diminish their capacity for rational judgement. In fact, it is evidence of rational deliberation that impoverished persons decide whether or not to take advantage of the opportunity to earn money as research subjects. If they decide to volunteer, however, this choice is determined predominantly, if not entirely, by the lure of financial gain. Altruistic goals of benefiting society and curiosity about biomedical research are unlikely determinants. Newton asserts with great idealism that it is possible to "...keep monetary inducements down to the point where they alone could not fully explain anyone's participation in the research."[105] *Macklin, more realistically, finds the expectation of subjects' identification with the goals of research*

to be "...at odds with what empirical evidence reveals about the nature of biomedical research."[106]

Macklin accepts that virtually all impoverished persons who participate in research are motivated by money and asserts that this motivation is dominated by poverty. This realism stops, however, where Macklin starts to argue that low socioeconomic status has ethically relevant effects on persons' decision-making capacity. She concludes that: "In the absence of coercing people, [protection of impoverished persons] does not properly count as [unwarranted] paternalism, but is rather an expression of another ethical precept: concern for the welfare of our fellow human beings."[107]

Macklin is making more a psychosocial appeal for humanism than an ethical argument. Whether or not "concern for the welfare of our fellow human beings" is the same as respect for persons, low socioeconomic status would have to be extreme to deny such integrity and responsibility and to cause such weakness of will that diminished autonomy becomes ethically relevant and justifies paternalism. Macklin implies that the behavior of underprivileged persons is practically an inevitable consequence of economic deprivation. Although it is reasonable that impoverished persons, in spite of welfare or unemployment benefits, are tempted to take advantage of large wages to become research subjects, it is not always causal that this temptation is undue.

Money is one of the ordinary seductions and temptations in normal life. There is little doubt that welfare recipients are willing to take greater risk than students or wage earners in order to secure money. However, it does not follow that impoverished persons participate in research that they do not consider to serve their own best interests. Respect for persons is not served by consigning impoverished persons to protection from large payments (and, therefore, from risk of injury) when they themselves retain the capacity to to deliberate about harms and benefits.

Offers of cash payment are not threats to participate in research. They are not coercive. Although restrictions on compensation are intended to be for the good of impoverished persons, (whether or not they agree that it is for their own good), unwarranted paternalism arises when these restrictions are placed on monetary inducements because higher sums are believed to impair the capacity of volunteers to judge the risks of participation in research. If a cash payment is not coercive, can the impairment of judgement of risk by impoverished persons be ethically relevant? Is cash payment ever tempting enough to be undue?

The answer to these questions is yes. However, research rarely satisfies the criteria for which payment is undue. These criteria are stringent. Given that potential research subjects include impoverished persons, the most important criteria include the highest acceptable risk

approved by IRBs and the payment comparable to a typical welfare or unemployment check.

Risk of Injury: The ethical principle of beneficence requires that research involving risk be justified on the condition of a favorable balance of harms and benefits. DHHS regulations stipulate that research should not be started unless "[r]isks to the subjects [are] reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[108] For research already in progress, DHHS regulations require that "[a]n IRB shall ...suspend or terminate approval of research ...that has been associated with unexpected serious harm to subjects."[109] IRBs are required to review all research protocols funded by federal agencies (Yale Medical School requires IRB review regardless of funding source).

For normal, healthy volunteers, however, the condition of a favorable harm-benefit ratio is necessary but not sufficient. The risk of injury in a protocol may be unjustified although the harm-benefit ratio is favorable (as when potential benefits to society are considered to be extremely great). Although IRBs protect subjects by disapproving or terminating research that presents an unfavorable harm-benefit ratio or an unreasonable risk of injury, this paternalism is justified. Only the various experts (clinical specialists and scientists, lawyers and clergy) found on IRBs can be expected to evaluate effectively the risk of injury in potentially harmful research.

Although IRBs disapprove those protocols presenting clearly unreasonable risk, they approve others presenting risk that borders on unreasonable. These latter protocols present what may be categorized as the highest acceptable risk of injury to research subjects; in addition, these are the protocols with ethical relevance to decisions about due and undue monetary inducements. A practical way of identifying protocols that present the highest acceptable risk may be to measure the amount of time IRBs devote to the discussion of potential harms. While IRBs devote relatively less time to discussion of risk that is clearly unreasonable or minimal, they devote substantial amounts of time deciding about risk that borders on unreasonable. If a protocol is determined to present the highest acceptable risk, then IRBs must give consideration to the expected population of research subjects. Based on the expectation of impoverished persons serving as research subjects, IRBs must be restrict monetary reward in order to prevent undue inducement to consent to risk of injury.

Size of Payment: In its regulations on research involving human subjects, DHHS stipulated no guidelines or instructions for determining when payments to normal, healthy volunteers are excessive. The regulations state only that: "Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as ... persons who are economically disadvantaged, [IRB approval requires that] appropriate safeguards have been included in the study to protect the rights and welfare of these subjects."[110] *Only this general statement*

is possible because of the broad range of vulnerablilty presented by different classes of persons. Each protocol must be considered in light of its predicted harms and expected subject population.

By definition, impoverished persons need money to purchase what they perceive are basic necessities of life. Extrinsic constraints notwithstanding, these persons attach greater value and utility to wages and to the opportunity to earn wages than do students, professionals and most other classes of individuals. The utility of payment may become so great that it outweighs the experience of physical harm, discomfort and even pain. The weight of this utility is ethically relevant and justifies the decision of impoverished persons to expose themselves to risk of injury. Payment is not undue because it provides relief that is needed desperately. Restriction of payment that is not undue limits the choices of autonomous agents and deprives impoverished persons of the opportunity to earn as much money as possible. It violates not only respect for persons but also a third precept of justice. As this precept is interpreted by Newton: "...[J]ustice demands that the opportunity to earn money by shouldering [research] burdens should be extended first to the least advantaged of the society."[111]

A monetary inducement can manipulate the vulnerability of impoverished persons and can impair their capacity of persons to judge risk of injury. Even if such impairment occurs, however, payment may be acting much as a bribe and may not necessarily be unjustified. In order for a monetary inducement to be undue, it must cause persons to

participate in research that presents either unreasonable risk (such as permenant disability and death) or the highest acceptable risk of physical or psychological injury and pain. If IRBs successfully fulfill their duty, vulnerable populations are protected from exposure to unreasonable risk. In the case of research presenting the highest acceptable risk, excessive payment is not justified. Vulnerable, impoverished persons are entitled to protection and the principle of respect for persons justifies restriction of size of payment.

The precise determination of what is justified payment depends on particular variables such as the duration of the protocol (whether research procedures extend over hours or over days) and the number of return visits (whether extra reimbursement is necessary to defray the cost of travel, meals and miscellaneous expenditures). These additional expenditures may be calculated protocol by protocol and may be added to some baseline payment that is pegged to a percentage of the standard, monthly welfare or unemployment check. Because these checks are often the largest sums of money with which impoverished persons come into contact, undue inducement would certainly include payment that equals or surpasses them.

Referring to the study of hepatic glucose uptake in normal, healthy volunteers, it is instructive to consider the criteria of highest acceptable risk and size of payment.

In this research, neither is the risk of injury unreasonable nor is the harm-benefit ratio unfavorable. Although this physiology study exemplifies a class of protocols presenting the highest risk that IRBs usually review (for normal, healthy volunteers), this study was approved based on the following statistics (and based on the policy that subjects receive free therapy for research induced injury). In the experience of the investigators:[112] *1) in over 4000 peripheral venous catheterizations, there were only twelve recorded episodes of thrombophlebitis; none of these episodes had known, significant sequelae. 2) in over 500 brachial and femoral arterial catheterizations, there were no significant complications; several patients experienced subcutaneous hematomas that all resolved spontaneously without sequelae. 3) on passage of the catheter through the right atrium, only an occasional patient experienced premature contractions; there had been no atrial or ventricular tachycardia and no requirement of anti-arrhythmic therapy. 4) the incidence of infection with hepatic venous catheterization was zero.*

In this physiology study, investigators proposed that volunteers should receive one hundred dollars. This monetary inducement, although substantial for only six hours of procedures, was approved by an IRB.[113] *One hundred dollars was considered to be not only low enough to avoid undue inducement of vulnerable persons, but also high enough to remunerate fairly for the risk of injury presented by the research procedures.*

CONCLUSION

Historical precedents of abuses of the voluntariness of vulnerable populations - prisoners during World War II, elderly patients at the JCDH, the mentally ill at Milledgeville, and uneducated blacks in the Tuskagee syphylis study - have magnified concern about the possibility of similar abuses of the voluntariness of impoverished persons. The tendency to ascribe the same dependency to the relationship between research subjects and investigators as exists in the relationship between patients and clinicians also has magnified concern about protection of impoverished persons. The objective of this discussion has been to identify ethically relevant criteria for distinguishing due from undue monetary inducements and, thereby, to demonstrate that the attention given to undue payment is warranted only under stringent criteria.

Many factors interfere with the autonomy of normal, healthy volunteers and impair their capacity to make a rational decision about participating in research. Important factors include the disclosure of information about the procedures of a protocol, its harms and benefits, the language used in the consent form, the interaction between investigator and potential subjects, and the setting and timing for obtaining informed consent. Attention to these factors relating to the consenting process most effectively maximizes the voluntariness of subjects to refuse participation in research. In general, IRBs should

devote more attention to the consenting process than to restrictions of cash rewards.

Research involving minimal risk or small increments above minimal risk is comparable to simple employment. If subjects are normal, healthy volunteers - whether impoverished, enrolled in a university, or employed professionally - they should receive unrestricted payment that may reflect market forces or the extravagant budget of investigators. Given minimal risk, size of payment is not ethically relevant to the violation of respect for persons and does not entitle persons with diminished autonomy to protection from impaired capacity to refuse participation. For research subjects, the bigger the inducement the better.

Research involving more than minimal risk of physical or psychological injury requires extra consideration by IRBs if the risk is determined to be in the highest acceptable category. Offers of large payment may cause vulnerable persons to lose the freedom to choose not to participate. Given that the potential subject population includes impoverished persons, investigators and IRBs must determine a payment that strikes a compromise between undue inducement and remuneration appropriate for exposure to possible discomfort, disability and pain. Restricted payment protects impoverished persons from irresistable temptation and causes them to deliberate more seriously about whether participation is in their best interests.

In research involving more than minimal risk, IRBs should review each protocol according to its own circumstances. Although the primary focus should be on the consenting process and on the restriction of material reward, IRBs also should be sensitive to the following considerations:

1) Payment should not be reduced to an amount that provides sufficient incentive for participation in research but insufficient remuneration. Unfortunately for impoverished persons, investigators, especially because of diminishing federal grant support of research, tend to offer as little payment as the market can bear. Therefore, as the probability and magnitude of injury increase, a gap occurs between the amount of money required to remunerate fairly for exposure to risk and that required to induce the participation of a sufficient number of impoverished persons. If subjects are exposing themselves to risk of discomfort and pain, this gap should be narrowed as much as possible.

2) Lowering payment cannot convert "wrong" reasons for participating in research into "right" reasons. Subjects of biomedical research volunteer primarily because of money and not because of benefit to society, identification with research goals or curiosity. As subjects become so financially deprived that they are willing to accept less payment, participation due to altruism becomes more questionable.

3) As payment is lowered, persons who need money and who cannot find alternative employment fill a greater percentage of the quota of

total research subjects required by a particular study. Because this quota is inelastic, more impoverished persons, including students, are paid less for exposure to the same degree of risk. This selection bias exploits impoverished persons and violates the precept of justice requiring equitable sharing of research burdens in society.

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