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# The Epistemic Necessity and Ethical Permissibility of Randomized Clinical Trials: A Minimalist Defense

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UNIVERSITY OF MIAMI

THE EPISTEMIC NECESSITY AND ETHICAL PERMISSIBILITY OF  
RANDOMIZED CLINICAL TRIALS: A MINIMALIST DEFENSE

By

Matthew A. Schuh, Sr.

A DISSERTATION

Submitted to the Faculty  
of the University of Miami  
in partial fulfillment of the requirements for  
the degree of Doctor of Philosophy

Coral Gables, Florida

December 2008

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RANDOMIZED CLINICAL TRIALS: A MINIMALIST DEFENSE

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The Epistemic Necessity and Ethical Permissibility  
of Randomized Clinical Trials: A Minimalist Defense

(Ph.D., Philosophy)  
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Abstract of a dissertation at the University of Miami.

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I argue for two main theses that are at odds with the positions of many clinical researchers and philosophers who write on the ethics of clinical research. The first is that certain types of clinical trials, namely, randomized clinical trials with double or triple blinding and a placebo group are generally necessary to establish that a medical intervention is effective in treating a certain type of disease or disorder. The second main thesis is that such trials are generally not ethically impermissible. My minimalist defense of clinical trials differs from most defenses of clinical trials found in the literature. I feel that the ethical permissibility of clinical trials can be judged by answering “yes” to the following questions:

- 1) Is the potential experimental subject competent to exercise his autonomy and his right of self determination in order to enroll in the clinical trial?
- 2) Is the potential experimental subject informed about the nature of risk and benefit involved in his participation in the clinical trial?
- 3) Is the trial scientifically/ epistemically valid?
- 4) Will the trial attempt to answer a scientific question or questions of value?

I argue that competent persons have the right to enroll in scientifically valid clinical trials so long as they are informed and consent to participate.

## **DEDICATION**

I dedicate this work to my wife and children. My wife, Aline: you are my other half, the only person in this world that makes me whole. My love, you have inspired me to reach far beyond my potential and to persevere in all things. You rescued me from the darkest of nights and have brought light to my life. It is the strength of our love that has seen me to this moment; I have no doubt that our love will see me through many more.

My children, Brianna, Matthew Jr., and Ava: You give my life purpose. I work, and strive, to better myself, so that I can provide each of you with all that you need- now and always. You are all a part of me, and I will always be a part of you. My love for all three of you is beyond words. I have been and always shall be, here for you. I have no doubt that each one of you will reach heights much greater than mine; I can only hope to provide each of you with the same measure of inspiration that you have provided for me.

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I must recognize two of the most important people in my life: my mother and father, Drs. Edward and Sandra Schuh. Poppy, after thirty-seven years of teaching philosophy at UM, gave me the following advice upon my enrollment at the university as an undergrad; he said, “Don’t study philosophy.” Although I have no doubt that he was sincere in his statement, I am glad that I went against his better judgment. My mother, on the other hand, has envisioned this moment since the day I entered graduate school. We discussed the epistemic necessity of RCTs ad nauseum. Although I normally disagree with everything she says, having her say it has helped to hone my arguments. Her criticism was essential to shaping this work into the final version that you hold in your hands.

One of the greatest influences upon my philosophical education was the late Dr. Ramon Lemos. Ramon my friend and he was my mentor. It was on his recommendation that I was accepted into the graduate program. It was under his tutelage that I focused upon social and political philosophy. I took every class he ever taught at least twice (as they were offered at various levels). As a result of this, I heard every one of his jokes at least three times. He was an invaluable



guide to me during my academic career- he is greatly missed by all of his students. He ingrained within me a deep appreciation for the history of philosophy. He also helped me to recognize the importance of faith to a man's soul. My only hope is that I may teach just long enough so that I may be just as politically incorrect within my lectures as he was in his.

I would also like to thank Dr. Risto Hilpinen, for his support throughout my academic career. He is never at a loss to provide a charitable interpretation of another philosopher's work. I am indebted to him for his help in reviewing several earlier drafts of the document. I believe that I have taken just as many courses with Risto as I did with Ramon. He passed on great philosophical insight within each and every one of his courses.

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All of these individuals, in no small measure, contributed to the completion of this dissertation. They all helped to mold the philosopher, and man, that I am today. I am in your debt always.

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## **Chapter 1: Epistemic Issues Regarding Randomized Clinical Trials**

### **Introduction**

There is an old saying: *seeing, is believing*. This piece of folk wisdom seems to have influenced the judgments of medical professionals for thousands of years. To many non-scientists, and naive empiricists, this statement might appear to be a tautology. Our language is filled with a myriad of such clichés. Another statement, "clinically proven" is in danger of falling into such a category. Just a cursory examination of the history of medicine demonstrates that many beliefs which are based upon careful observation (without further experimental or theoretical evidence) generally turn out to be false. The real world is much more complicated than is supposed by most critics of clinical research. Basing our beliefs regarding the efficacy of medical interventions upon observation alone is not sufficient to confirm those beliefs. When the human element, including our subjective experience, is put into the equation the issue of establishing the efficacy of medical and psychological interventions becomes more complicated.

An examination of historical records shows a plethora of medical interventions that were once in vogue with medical practitioners which did not stand the test of time. These interventions were believed to have worked but ultimately they did not. Although these "remedies" were administered for hundreds, and in some cases thousands of years, many of them were not effective in curing the underlying ailments. It has been said that "the history of medicine is really the history of the placebo effect."<sup>1</sup> The notion of the placebo is of great importance to this inquiry. The fact that patients often get better simply because

they expect to, regardless of the efficacy of a medical intervention, raises significant challenges in clinical research. The phenomenon of the placebo effect which can be defined as patient improvement when given a causally inert treatment is so wide spread that it is even found in HIV clinical trials.

One challenge is to recognize that, seeing is not always grounds for believing. If certain procedures are not followed, if steps are not taken, then the validity of the results of a clinical study can be called into question. In many cases patients appeared to improve as a result of the given medical intervention, yet under closer examination they did not. Not until the middle of the 20<sup>th</sup> century had experimental designs matured to a point where many of the interventions could be confirmed or disconfirmed in an experimentally significant way.

What these cases illustrate is that all evidence is not equal. In fact, it will be argued that some “evidence” is not evidence at all. What actually takes place in the real world does not easily fit into our intuitive preconceptions. To the layperson confirmation of the efficacy of a medical or psychological intervention might seem as simple as administering a treatment and seeing if the patient gets better. *Prima facie*, if the patient improves, the treatment must work. To the layperson, the treatment must be the reason why the patient’s symptoms went away. The treatment must be efficacious in curing your ailment; after all: *seeing, is believing*. Yet, after careful consideration, there are a myriad of other possible explanations as to why a patient improved; not just that the intervention works. As the issue of efficacy is examined, its complexity becomes clear. I argue that it is necessary to isolate the variables in such a way as to establish a causal

connection between the treatment under consideration and effects to the patient. This is a standard position among statisticians, but it is often lost in the discussion of the epistemic need for clinical trials by physicians, researchers, and philosophers. If the experimental design is such that it does not allow for a differential analysis (allow for one to isolate the cause of an observed effect) between plausible variables, then the data collected cannot confirm the intervention under consideration. Again in order to confirm the medical intervention the evidence must be sufficient to rule out legitimate rival hypotheses. If the experimental design cannot rule out legitimate rival hypotheses then the data cannot be used to confirm the intervention under consideration. In my view, after careful consideration, there is only one type of experimental design that allows for a differential conclusion among possible causal variables: the Randomized Control Trial, RCT.

### **Purpose of Dissertation**

I intend to argue for two main theses that are at odds with the positions of many clinical researchers and philosophers who write on the ethics of clinical research. The first is that certain types of clinical trials, namely, Randomized Control Trials with double or triple blinding and a placebo group are generally necessary to establish that a medical intervention is effective in treating a certain type of disease or disorder. There are some exceptions to this rule and they will be discussed later. For the present, however, it is enough to say that in virtually all cases of proof of efficacy of pharmaceutical treatments at least, Randomized Control Trials with at least double blinding and placebo controls are epistemically

necessary for establishing efficacy. In the literature this view has been branded placebo orthodoxy<sup>2</sup>. Arguments against this view will be considered and dismissed.

The second main thesis is that such trials are generally ethically permissible. They may be ethically impermissible in certain types of cases, for example where informed consent is not obtained, but not merely, as some have claimed, because they involve random assignment of subjects to treatment and control groups or because they employ a placebo group. It is also argued that trials are unethical if they violate the notion of equipoise. It is often argued that a state of uncertainty (equipoise) between the new intervention and the standard of care, as to which is superior, must exist in order to justify employing experimental subject in a clinical trial. It is claimed that if such a state does not exist, then the physician/researcher has violated his therapeutic obligation to the patient/experimental subject by employing him in the clinical trial. I will examine this idea in detail and deny that it is a necessary requirement. I feel that the ethical permissibility of clinical trials can be judged very simply by answering “yes” to the following questions:

- 1) Is the potential experimental subject competent to exercise his right of self determination in order to enroll in the clinical trial?
- 2) Is the potential experimental subject informed about the nature of risk and benefit involved in his participation in the clinical trial and provided their voluntary informed consent?
- 3) Is the trial scientifically and/or epistemically valid?
- 4) Will the trial attempt to answer a scientific question or questions of value?

There is more to be said about all of these issues, but I argue that competent persons have the right to enroll in scientifically valid clinical trials so long as they are informed and consent to participate. My minimalist defense of clinical trials differs from most defenses of clinical trials found in the literature. I eschew other ethical “requirements” such as equipoise, a favorable risk/ benefit ratio and independent review of research protocols.

In discussing the relevant ethical issues, both philosophers and non-philosophers have tended to use either one of two strategies: the first is to appeal to some general moral theory, usually Kantianism or Utilitarianism; the second is to appeal to medical codes of ethics that have been developed by expert ethicists. I reject both approaches. I employ a minimalist approach that does not presuppose the truth of any broader moral theory such as either Kantianism or Utilitarianism. I do take for granted that people have some basic, prima facie rights, but this presupposition does not necessitate the truth of any other more general ethical theory such as Intuitionism or Natural Rights theory. I try to show that the appeal to a very abstract moral theory such as Kant’s or Mill’s is inadequate. In the place of these theories, I rely on two notions: informed consent and patient autonomy. Use of these notions is not new, but how I develop them differs from the standard accounts. Other conditions that are often employed such as equipoise are not necessary for the ethical permissibility of clinical trials. As to the second standard strategy, I discuss the appeal to ethical codes in chapters 4 and 5.



There are two additional, more difficult issues that I also discuss. Even if it is generally ethically permissible to use Randomized Control Trials, is it obligatory? I do not wish to claim that it is in all cases, but given their epistemological superiority it is obligatory in most cases to employ Randomized Control Trials to confirm the efficacy of most medical and psychological interventions.

The second issue is: Even if RCTs are necessary for proof of efficacy, are they sufficient? It has been said that, “Only randomized treatment assignment can provide a reliably unbiased estimate of treatment effects.”<sup>3</sup> The estimate of treatment effects in turn can be employed to determine efficacy. I believe that RCTs are a necessary part of the confirmation process. RCTs are a valuable tool; they are able to remove a great deal of ambiguity from clinical research. If a RCT is conducted, and well run, then we are in position (all things being equal) to determine the efficacy of the intervention under consideration. The same cannot be said of other types of clinical designs. A positive result gained by means of an observational study does not provide overwhelming evidence in favor of the supposed medical intervention- in most cases observational studies are neither necessary nor sufficient to confirm the efficacy of a medical intervention. The history of clinical research demonstrates that a positive result from an observational study is much less certain to stand the test of time as the same positive result from an RCT. One way to put it is this: there are many less false positives when RCTs are employed as compared with other types of clinical methodologies. What is clear, when one examines the historical evidence, is that the results of earlier RCTs are usually very accurate. It appears that when

properly designed and executed the treatments that have been confirmed by RCTs have, in fact, worked, whereas the treatments confirmed by earlier observational studies have often been disconfirmed by further investigation- usually a RCT.

On the surface this may appear to be a circular justification, but I do not believe that this is the case. Given the empirical evidence, I believe we are justified in ascribing to the results of RCTs superiority in epistemic quality. Numerous RCTs have been employed to confirm a myriad of medical and psychological interventions, and those results have seldom been demonstrated, upon later review, to be wrong. RCTs have been demonstrated to be a reliable method for obtaining beliefs about the effectiveness of medical interventions whereas the beliefs obtained by means of other methods, including observational studies, have been shown to be much less reliable. Since this is the case, we are justified in drawing the inference that RCTs are of greater epistemic value. The results obtained from other sorts of trials, particularly observational studies, cannot stake such a claim regarding the accuracy of their results. Historical records show that numerous interventions that were “confirmed” by means of observational studies were eventually shown to lack efficacy. RCTs are the gold standard in clinical research for a reason, in most cases they cannot be replaced or supplanted by other clinical research methodologies without a corresponding drop in the accuracy and reliability of the results of the research. Knowledge claims that are based upon data collected from other types of experimental designs very often turn out to be false.

For more than two thousand years, physicians were employing observation as the primary means of assessing medical interventions, and what history demonstrates is that most of the medical interventions that were employed and developed during this time turn out to be worthless; even though observation had seemed to confirm that they were effective. Only a handful of medical interventions were developed and later confirmed to be effective prior to the twentieth century. More than two thousand years of employing observation studies as the main (gold standard) for judging the efficacy of medical interventions resulted in little more than a state of quackery in medicine.

In the centuries before RCTs the best medicine could offer was potions, poisons and evasive procedures that were often no more effective at treating the underlying ailment than a sugar pill. Unicorn horn (also known as alicorn) was an accepted medical treatment for everything from headaches to impotence for hundreds of years! (Notwithstanding that there are no such things as unicorns). One could argue that medicine has moved from an art to a science as a direct result of the use of RCTs to test and confirm the efficacy of medical interventions. The exponential rise in effective pharmaceutical interventions appears to correlate perfectly with the adoption of RCTs in the confirmation process. It should be apparent, to those who consider this issue, that if we want to answer questions about efficacy of medical interventions, then RCTs are necessary all things considered, to accomplish this goal.

### **Historical Issues**

In the past 50 years, there have been many disagreements among physicians, clinical researchers, philosophers, and the lay public about the use of experiments involving human subjects. Opponents of Randomized Control Trials argue that clinical trials involving sick people are generally immoral because the physician has a therapeutic obligation to provide the optimal treatment to his patients. It is argued that if randomization is employed then that it is the equivalent of flipping a coin with treatment options instead of choosing the optimal treatment, and that if a placebo is used, then that is the same as using no treatment at all. Prima facie, these considerations are correct, but that is because the situation has been oversimplified. In practice there is not always an effective standard treatment, nor, where there is an established standard treatment, does the standard treatment always work for all patients. As such, it might be entirely compatible with a physician's therapeutic obligation to employ randomization or a placebo control even if we were to accept the notion of therapeutic obligation at face value.

I will grant that if the standard treatment is effective for a particular patient then the physician should not request that a patient enroll in either a RCT or PCT, yet I feel each patient has the right to enroll in a clinical trial, even if the standard treatment works. The decision to enroll in clinical trials should remain in the hands of the patient not the physician. I feel the patient's rights supersede the physician's obligation of care in this situation. Physicians ought not to act paternalistically by withhold the possibility of participating in a RCT or PCT from their patients. It is a violation of the rights of patients to refrain from offering

them the possibility of enrolling in clinical trials. As a further point, even if the standard therapy is effective for a patient, it may come at the cost of severe side effects. Some patients may be willing to enroll in clinical trials, and possibly receive a placebo, for the chance to receive or help develop a new, effective therapy with lesser side effects. The reality is that few patients will consider enrolling in a clinical trial if the standard treatment is effective for their condition, but, ultimately, it is their decision to make. The fact that few subjects would enroll in a clinical trial does not give the research the right to violate their rights under the guise of scientific advancement or the common good. Furthermore, if there is an effective standard treatment, and it does work for the patient, then they would most likely be unwilling to enroll in any type of trial regardless of whether or not it was an RCT or an observational study.

Historically, some of the controversies about clinical trials developed because of experiments that were pretty clearly outrageous from a moral point of view. Many were conducted by Nazis scientists. In this country, the most notorious experiment is the Tuskegee study in which black men with syphilis were left untreated apparently for experimental reasons. Some of these individuals developed complications as a result of the disease and died as a consequence.

Although informed consent is obtained in most research, it is not obtained in all cases. Informed consent must be received from the experimental subject, in almost all cases, in order for the clinical trial to be ethically permissible. It is a fundamental obligation of clinical researchers to obtain the informed consent of their experimental subjects. Clinical trials that are conducted without obtaining

informed consent are unethical (in all but rare cases). It might seem obvious that informed consent should be received before experimenting upon a subject, but there have been many experiments conducted where this has not happened. From 1932 till 1973 the United States Public Health Service conducted a clinical study without informed consent on African American sharecroppers who had syphilis.<sup>4</sup> From 1932 till 1973 the United States government experimented on several of its citizens. African American sharecroppers were used as research subjects without their knowledge or consent. This study is now known as the Tuskegee syphilis study.

In this study men, who had previously contracted with syphilis, were studied. They were given “free” medical care and were discouraged from seeking treatment elsewhere. Although most of the experimental subjects believed that they were receiving treatment for their condition, the doctors were simply recording the progression of the disease. The progression of the disease ultimately leads to blindness and insanity.<sup>5</sup> When the study commenced there was no effective treatment for syphilis, but by 1947 penicillin had been shown to be effective and was widely available and accepted as a treatment for the disease. Although there was an effective treatment for this debilitating disease, the study was continued for decades without administering a cure for the participant’s condition. The fact that this study was sanctioned by the United States government and continued for some twenty-five years after a cure was recognized is morally abhorrent. Public awareness of this study eventually led to greater oversight and regulation of clinical research in the United States.

Even with public awareness of this issue and increased regulation, studies are still conducted, (with the sanction of the FDA), without obtaining informed consent. One of the most recent of which took place from 2004- 2006.<sup>6</sup> In 27 cities across the United States, seriously injured accident victims were used as test subjects in a medical experiment involving artificial blood, without their knowledge or consent.<sup>7 8</sup> In many cases where informed consent has not been obtained it seems that few, if any, of the experimental subjects would have given their informed consent if they had been asked to do so. Many of the defenders of trials that are conducted without obtaining informed consent often employ ad hoc excuses as to why it is necessary to conduct clinical trials upon unsuspecting subjects without obtaining their informed consent; none of these “defenses” stand up to scrutiny. Everyone one of these trials could have been conducted by obtaining informed consent. When pressed, some scientists admit that the trials could not have been conducted because no one would have willing consented to participate in the trial! As noted earlier, the inability to obtain informed consent from a sufficient number of experimental subjects does not legitimize violating the informed consent requirement. Generally, waving informed consent is a violation of the experimental subject’s rights. This violation of rights results in the research project being unethical.

Less famous cases discussed in the literature include the use of high levels of oxygen in treating premature infants<sup>9</sup> and the case of Dr. Jones’s treatment of burn victims in India.<sup>10</sup> In the premature infant’s case it was believed that by saturating premature infants with high levels of oxygen that they would have a

better chance of survival, yet evidence began to accumulate about a terrible side effect: blindness. It appeared that the high amounts of oxygen had the unfortunate side effect of retrolental fibroplasias a condition that eventually leads to blindness. In order to explore this issue a clinical trial was conducted to determine whether or not this was actually the case. In the trial 36 premature infants were given high doses of oxygen while a control group of 28 infants were given low doses. In the end, it was demonstrated that high doses of oxygen was a causal factor in the infants going blind. Unfortunately, this trial resulted in the permanent blindness of eight of the infants involved. Trials of this type, although epistemically sound, raise significant ethical questions.

In the Jones case he conducted clinical trials in India upon individuals with severe burns. Jones believed that because of their injuries the victims were more susceptible to pseudomonas septicemia. He employed a vaccine against the disease. Early clinical results demonstrated that burn victims which were given the vaccine had a survival rate of nearly 100%, whereas the survival rate for those given a placebo or no treatment was about 40%. Even with these results in hand, the trial was continued. Ethical commentators have criticized the continuation of the trial, given such positive dramatic results. Generally, I agree with this criticism especially in a case such as this. In cases where there is such a positive dramatic result, it might be ethically required that a clinical trial be suspended and that all experimental subjects be given the medical intervention. Yet stopping a trial early can also lead to problems.



Sometimes early results seem to indicate effectiveness in the particular class of patients under consideration, when, in fact, the treatment is ineffective in the long term. This was the case with a preliminary AZT trial run in the United States.<sup>11</sup> A randomized, placebo control trial was run for one year. An analysis of the data showed that test subjects in the control group who were receiving a placebo, were approximately 2.5 times more likely to have acquired human immunodeficiency virus (HIV) than those receiving treatment (AZT).<sup>12</sup> Later studies showed that after 18 months the benefits of the treatment were lost, and the treatment group performed no better than the placebo group.<sup>13</sup> In other words, stopping early can lead to misleading results, and in some cases invalidate the results of a trial.

HIV research has been one of the most controversial and discussed types in the recent literature. In the 1990's, there was also much debate about the AZT trials designed to prevent maternal-infant transmission of HIV. A lot of the controversy arose because the experiments contained a placebo control and were carried out in developing countries in Africa and Asia. The subjects were generally poor women who had contracted HIV. Some received AZT and others received a placebo. There was an added risk of death to children of the pregnant women in the placebo group. In fact, a subsequent analysis of the actual results showed that significantly more placebo babies contracted HIV than the AZT babies. Because the primary purpose of the experiment was not to benefit the subjects or their children but to obtain scientific knowledge that would be useful to other women, some argued that the experiments were unethical. The fact that the subjects were poor women in poor countries added to the controversy. Another issue was raised by Lurie and Wolf

(1997) in an article in the *New England Journal of Medicine*. They argued that the experiments were not needed because there already was sufficient evidence concerning the proper dosage of AZT to be used in maternal-infant transmission of HIV.

The poor and uneducated are often employed as guinea pigs for Western medicine. As an example, in 1996 the American pharmaceutical giant Pfizer used the advent of an outbreak of meningitis in Nigeria to justify running a trial of their new drug Trovan on children afflicted with the disease.<sup>14</sup> Pfizer argued that it had to act quickly in order to save lives, but in all actuality they were working quickly only so that they could promote their goal of testing the drug on a pediatric population. A class action lawsuit was eventually filed by 30 families of children involved in the trial. Most had not understood the nature of the research. Further most did not understand that the clinical trial involved an experimental therapy. The implications of this type of research will be considered as we examine the Declaration of Helsinki and other moral codes in chapter 4.

This last point raises a more general issue that has developed in the literature on the ethics of experimentation. Scientific issues, which I will refer to as “epistemological issues”, have been intertwined with the ethical issues. In a famous paper published in the *New England Journal of Medicine*, Rothman and Michels (1994) argue that experiments with a placebo control are unethical. Part of their reason is that, on their view, such controls serve no necessary epistemological purpose. They argue that a best treatment comparison (Active Control Trial, ACT) without a placebo control can serve the same purposes as a placebo comparison

(Placebo Control Trial, PCT). However, they also argue that even if this were not true, designs using placebo controls would still be unethical in all cases.

After the publication of the Rothman and Michaels's paper, a worldwide debate ensued among physicians and researchers in the World Health Organization about the ethics of placebo controls. This is hardly, however, the only issue. Even if placebo controls are not employed, many object to any sort of randomized control trial (RCT) either on the grounds that they are epistemically unnecessary and even, some would argue, insufficient for establishing efficacy, or because they are unethical whether or not they serve a useful scientific (i.e. epistemic purpose).

### **Epistemic Thesis**

My objective in this chapter is to show that Randomized Control Trials (RCTs) address compelling epistemic issues better than other types of experimental designs. **The Epistemic Thesis that I defend is as follows: Clinical trials employing the elements of Randomization, Double Blinding, and Placebo Control are all necessary in most cases to establish the efficacy of most medical and or psychological interventions.** I argue that confirmation must be differential, and that if the rival hypotheses cannot be ruled out by the experiment, then the data provide no evidence in favor of the efficacy of the intervention. In general, RCTs are necessary for confirmation because they can accomplish this.

In brief, randomization is necessary to eliminate the possibility of selection bias. Controlled conditions are necessary to establish a causal relationship between the proposed intervention and the effect on a patient. Without conducting

an experiment in a controlled setting, the skeptic can rightly challenge the efficacy of the treatment because one cannot be certain that some unknown variable was the cause for the patient's improvement. In other words, the controlled setting allows the experimenter to gather data that can differentiate among the possible causal variables to confirm the efficacy of an intervention. Yet a controlled setting is not enough. This is because a controlled setting does not rule out the possibility of the placebo effect.

In conjunction with randomization, a feature known as "blinding" helps ensure that the experimental subject's expectations do not distort the conduct of a trial or the interpretation of its results. Single-blinding means the participant does not know whether he or she is receiving the experimental drug, an established treatment for that disease, or a placebo. In a single-blinded trial, the research team does know what the participant is receiving. A double-blind trial means that neither the participant nor the research team knows during the trial which participants receive the experimental drug. Triple blinding means that no one including the physician, the patient, or the statistician knows who received the active substance and who received the placebo.

In my view RCTs, specifically placebo control trials (PCTs), can avoid several skeptical objections that other types of clinical trials cannot. Some patients respond to inactive treatments. The exact number of patients who respond in this way to inactive treatments is indeterminate. Patients who respond to inactive treatments are having a placebo response to the treatment; this is also known as the placebo effect. Given that some patients will respond to inactive,

and therefore, ineffective treatments, a placebo control group is normally necessary to establish the efficacy of a medical intervention.

As the placebo effect is almost always a possibility when conducting a clinical trial it is a necessary that it be accounted for. One (and perhaps the only way) to account for the placebo effect is to employ a placebo control group. I argue that a placebo control group is necessary, (in almost all cases), in order to establish the efficacy of an intervention. If an intervention cannot outperform the placebo control group, then there is no basis upon which to claim its efficacy.

It might be the case that a particular intervention could be tested against a standard therapy, and not a placebo control group, in a particular experiment and one could still establish efficacy, but this can only be done if the standard therapy has been tested against a placebo control. As such there should be some measure of transitivity between trials.

### **The Purpose of Clinical Research**

What is the goal of clinical research? More specifically, in this context, why conduct clinical trials? Some argue that experimentation is necessary in order to acquire scientific knowledge. A phrase that is often stated in advertisements for medical interventions is “clinically proven”. I agree with this assessment.

Clinical trials are often conducted to confirm the antidotal, non experimental observations of physicians working in the therapeutic setting. New interventions are often employed by physicians when the standard therapy proves ineffective for their patients. Over time, the evidence accumulated in favor of the effectiveness of the intervention may warrant conducting a RCT to confirm its

efficacy. I believe that clinical trials must be conducted in order to confirm the efficacy of most medical interventions. Clinical trials are a means of conducting investigations and of collecting observations. Sets of observations (data, evidence) are collected under controlled conditions in order to confirm (verify, justify, authenticate) a given hypothesis regarding a medical intervention. The data collected can then be organized and categorized in order to draw inferences and conclusions. If the data are not collected by means of an epistemologically sound methodology then they provide no evidence for or against a purposed intervention. There has been a great debate recently as to which research methodology is the best.

### **Definition of Clinical Trials**

Broadly speaking a clinical trial is a research study, employing human volunteers, designed to answer specific medical or psychological questions. According to the FDA, “A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are the safest and fastest way to find treatments that work in people, and new ways to improve health.”<sup>15</sup> Clinical trials are normally experimental in nature; trials are conducted in order to test a particular hypothesis. The results of such trials are often used to make a generalization regarding the effectiveness of the medical intervention in the entire population as a whole. There are different kinds of clinical trials, including those used to study: prevention options, new treatments or new ways to use existing treatments, new screening and diagnostic techniques, options for improving the quality of life for people who have serious medical conditions.

“Clinical trials are conducted according to a plan called a protocol. The protocol describes what types of patients may enter the study, schedules of tests and procedures, drugs, dosages, and length of study, as well as the outcomes that will be measured.”<sup>16</sup>

Usually clinical trials compare a new product or therapy to the current treatment to see if it works as well or better in treating or preventing a disease or condition. In a blinded study, a participant may be randomly assigned to receive the test product, or an existing, approved therapy. In some studies, participants may be assigned to receive a placebo (a product with no therapeutic action that looks and may cause effects similar to the test product). The definition of the term placebo is highly contentious. At present, I will leave this aside, returning to it when we consider RCTs with a placebo control.

Even though the definition of what it is to be a “placebo” is not settled, according to the FDA, comparison with a placebo can be the fastest and surest way to demonstrate therapeutic effectiveness of new products.<sup>17</sup> Clinical trials can be used in order to determine certain preventative options, develop new treatments, find new ways to use existing treatments, create screening test and diagnosis techniques, and for managing chronic illness with new palliative therapies.<sup>18</sup>

### **Hierarchy of Evidence**

The FDA endorses a hierarchy for the evidence obtained from clinical research studies that places RCTs above all other trial types. On some readings of the FDA

regulations, once the safety of a compound has been established, one well designed RCT is sufficient to establish the efficacy of a new medical intervention.

**TABLE 1.1- Hierarchy of Clinical Trial Designs**

<b>GRADES OF EVIDENCE FOR THE PURPORTED QUALITY of STUDY DESIGN.</b>
<b>I Evidence obtained from at least one properly randomized, controlled trial.</b>
<b>II-1 Evidence obtained from well-designed controlled trials without randomization.</b>
<b>II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</b>
<b>II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.</b>
<b>III Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.</b>

In general, I agree with the gradation of evidence as described in the above table. Peter Jepsen paints the difference between RCTs and observational studies as follows:

In an experimental study- that is, a randomized controlled trial (RCT) - the investigator experiments with the effect of the exposure by assigning exposure to a random sample of study subjects. In an observational study, on the other hand, the investigator can only observe the effect on the exposure on the study subjects; he or she plays no role in assigning exposure to the study subjects. This makes observational studies much more vulnerable to methodological problems, so it is only reasonable that RCTs are considered the best way of proving causality.<sup>19</sup>

In order to defend my view, I will examine four reasons for association that can lead to unreliable inferences as a result of employing one of the lesser design methodologies. As each type of trial is considered it will become apparent as to why RCTs are held in such high epistemic regard.



### **Four Reasons for Association**

In a clinical trial researchers attempt to establish a correlation or association between the exposure to a particular intervention and an outcome. “There are four principal reasons for associations in an epidemiological study: bias, confounding, chance and cause. An essential aim of the design and analysis phases is to prevent, reduce, and assess bias, confounding, and chance so that a causal unbiased association between exposure and outcome can be estimated”<sup>20</sup> These same outcomes are also possibilities in clinical studies. Researchers could conclude that a medical or psychological intervention worked, when, unbeknownst to them, any of the reasons mentioned above might account for the results. As such, each will be considered in turn.

### **Types of Bias**

The experimenter effect is the biasing effect on the results of an experiment caused by expectations or preconceptions on the part of the experimenter. This is also known as experimenter bias. This type of bias can happen in clinical research when an outcome of an experiment tends to be skewed towards a result expected by the human experimenter. The inability of a human being to remain completely objective is the ultimate source of this bias. Double blind techniques are often employed to combat the bias.<sup>21</sup> The use of blinding can reduce or eliminate the experimenter effect. This will be explained in detail below.

Selection bias occurs if the selection process introduces another, unintended systematic difference between the study and control group. One way to avoid selection bias is randomization. Research studies that are not randomized are, in

principle, inherently biased. However, the use of randomization does not preclude selection bias. If the inclusion and/or exclusion criteria for the study are too restrictive, this may result in a type of selection bias. If the criteria are too restrictive, (and only certain groups are employed), this may lead to a result that is not externally valid. It will not be externally valid because the result will not be generalizable to the populous.

Another type of bias is known as information bias. Information bias results when there is an error measuring or recording an outcome. This sort of bias is a possibility in all types of research. It is certainly possible that the data collected are not recorded accurately regardless of the research methodology. Given that information bias is possible in all types of research, care ought to be taken by all researchers to minimize its effect on the data collected. It is important to consider the accuracy of the data collected and how they are recorded given that information bias is possible across all experimental methodologies.<sup>22</sup>

A final type of bias to be considered is systematic bias. An example of systematic bias would be a thermometer that always reads three degrees colder than the actual temperature because of an incorrect initial calibration or labeling, whereas one that gave random values within five degrees either side of the actual temperature would be considered a random error.

Once detected and quantified, it may be easy to compensate for a systematic bias. In the example just given, the researcher knows that the thermometer always reads three degrees below the correct value. Thus, the researcher can simply make a systematic correction by adding three degrees to all readings. In other cases,

while a systematic bias is suspected or even detected, no simple correction may be possible because it is impossible to quantify the error. Random errors can in some cases be reduced by repeating the experiment several times and considering an average result; in other cases repetition is not possible.

The existence and causes of systematic bias may be difficult to detect without an independent source of information; the phenomenon of scattered readings resulting from random error calls more attention to itself from repeated estimates of the same quantity than the mutually consistent, but, incorrect results of a biased system.

### **Confounding or Chance (Randomness)**

Confounding results when the measured effect our outcome is not the result of the exposure or medical intervention under investigation, but is the result of some other cause.<sup>23</sup> Chance is the notion that there may be some unknown and underlying reason, other than the medical or psychological intervention under consideration, of the observed effect. The estimate of the association between exposure and outcome is usually expressed as a confidence interval (usually 95% confidence interval). “The confidence interval can be interpreted as the interval which, with a 95% certainty, holds the true value of the association if the study is unbiased. Consequently, the wider the confidence interval, the less certain we are that we have precisely estimated the strength of the association. The width of the confidence interval is determined by the number of subjects with the outcome of interest, which in turn determines the sample size.”<sup>24</sup>

A lurking variable is an extraneous variable that affects the dependent variables in question but either has not been considered or has not been controlled. The confounding variable can lead to a false conclusion that the dependent variables are in a causal relationship with the independent variable. Such a relation between two observed variables is termed a spurious relationship. An experiment that fails to take a confounding variable into account is said to have poor internal validity.

### **Cause**

Establishing causation is the main goal of clinical research. Philosophically the notion of causality is highly contentious. In 1912 Bertrand Russell went so far as to claim that the notion of cause was a “relic of a bygone age.”<sup>25</sup> Russell argued that the notion of causality is not employed in the sciences. An examination of the current scientific literature shows this thesis to be false; if we are to narrow our scope to the medical sciences, then the term cause is employed regularly. Implicit in this idea of “clinically proven” is the notion that a given intervention plays a causal role in the treatment of an ailment. An effective treatment must play a specific (causal) role in the improvement of the patient’s condition. As opposed to an ineffective treatment that has no effect upon the condition, or a placebo treatment that leads to patient improvement for nonspecific factors that have no causal connection or physiological effect upon the patient’s condition. In order for a treatment to be effective, it must play a causal role in the patient’s improvement.

In most cases a medical intervention is confirmed if, and only if, it has been tested by means of an experiment that includes randomization, double blinding, and a placebo control. All of these elements are necessary in most cases establish

the efficacy of a treatment. The reason why experiments must always include all of the above mentioned features is that the skeptic can mount a legitimate challenge against a casual inference based on data collected from either observational studies or comparative trials of “best treatments” that may lack one or more of those features. Lacking any one of the above mentioned features calls into question the data collected from the trial.

Let us consider what might seem a relatively simple example: If I were to test a new drug for hypertension, I could establish a baseline blood pressure for the subject, administer the drug, and recheck the blood pressure. Presumably this is how the data would be collected in most experiments, including RCTs. In this case, if the patient’s blood pressure goes down, then surely there must a causal connection between this fact and the administration of the drug. Is not the most reasonable explanation of the facts to claim that the drug caused the patient’s blood pressure to go down? At this point, it might seem reasonable to assent to the notion that there must be a causal connection between the drug and this particular patient’s blood pressure; nevertheless this would be a mistake. The skeptic will maintain that the data in this case do not count in favor of the drug because it cannot rule out either the possibility of a placebogenic effect or spontaneous reduction in the patient’s blood pressure.

An important point, one that is often overlooked in this area by nonscientist, is that with observation alone, without other evidence, it is nearly impossible to establish that the drug is the cause of the reduction in the patient’s blood pressure. Because the drug is not administered in a controlled, experimental setting there

may be a lurking, unknown variable that is causally significant. One alternative explanation of the observational data is that simply being in a medical setting, in the presence of the doctor, helps to relax the patient, thereby causing a reduction in his blood pressure. The data in this case do not favor one hypothesis over another. As such, the data do not count as evidence in favor of the drug.

What if I administer the drug on 500 different occasions, and get the same result every time? Am I not warranted in concluding that the drug is effective in reducing the patient's blood pressure? If there existed other data, such as pharmacodynamics data of how the drug was metabolized in the body, it could be used to correlate the level of the drug in a patient's blood stream and his blood pressure, and then, collectively, all of the data might warrant drawing the inference that the drug works *for this particular patient*. It is important to note that there is evidence, beyond mere observation, in support of the drug's efficacy. The justification for the claim of efficacy for the intervention for is more than simply observation alone. Observational evidence is of the lowest and poorest quality as will be discussed below.

Nevertheless, even if a researcher were justified in drawing the inference in this particular patient that there is a causal connection between administering the drug and the patient's blood pressure going down; he could not conclude (would not be warranted in rendering the inference), that the drug will work in other patients since the drug has not been administered to enough individuals with the same condition.

Now if we were to extend this example to a group of 500 patients, and found similar results, then could it not be claimed that the data support the inference that the drug is effective? The answer is no, because all the data could be the result of selection bias, confounding with unknown factors or variables, a placebo effect, or even spontaneous remission. The data do not provide evidence in favor of the efficacy of the drug because it cannot rule out these other possibilities. If confirmation must be differential, and the revival hypotheses cannot be ruled out by the experiment, then it will be argued that the data provide no evidence in favor of the efficacy of the drug.

Even with a larger sample size, this type of observational design allows for the possibility that the results were obtained because of chance, confounding, bias or some unknown variable. It is true that these epistemic concerns are all possibilities for RCTs, the difference is they are much less likely to occur in a well run RCT, whereas they are nearly impossible to be control in an observational study. Few opponents of the necessity challenge the epistemic merit of RCTs, rather they usually maintain that most well run observational studies are of equal epistemic worth. For the consideration mentioned above, I think this is a mistake. RCTs and observational studies are not on equal epistemic footing. Observational studies are open to skeptical objection on numerous grounds, and the objections themselves have a reasonable foundation. These are not outlandish skeptical considerations. The skeptic that raises concerns about observational studies is not asking us to posit Descartes' demon world, whereas the skeptic of most well run RCTs is.

It follows then that there is an epistemic reason why such a study must always include randomization, blinding and placebo control. In most cases, if an experiment does not employ these elements, then any inference drawn from the results will be open to skeptical challenge. It follows that in the vast majority of cases, RCTs are epistemically necessary to confirm the efficacy of a treatment.

There are certain, rare cases where the preponderance of evidence gleaned from observation or other sorts of experimental methodologies is so great that one need not confirm the efficacy of a medical intervention with a RCT. Alan Kazdin discusses such a possibility in a 1981 paper on the subject.<sup>26</sup> Ed Erwin expands upon his view as follows: “I do not think, and Kazdin may agree with this point, that very many clinical case studies (observational studies) can be improved to the point that all credible rival hypotheses can be ruled out except the causal hypothesis of interest.”<sup>27</sup> In general, cases where observational evidence is on equal epistemic footing with RCTs are few and far between. One example may be the dramatic effect that introduction of penicillin had upon various diseases. The discovery of a drug like penicillin is extremely rare. Normally the statistical difference between an efficacious medical intervention and an ineffective medical intervention is very small. In other words, the results are not very dramatic. Normally a RCT will be the only way to confirm the efficacy.

### **Types of Clinical Trials**

Different types of experimental designs raise unique epistemic issues. Some of the most prevalent types of experimental design include: Historical Control Trials (HCT) which are sometimes termed observational studies, Randomized Control



Trials (RCT), Active Control Trials (ACT), Placebo Control Trials (PCT), and Pre- Randomized Control Trials (pre-RCT).

**TABLE 1.2- Types of Clinical Trial Designs**

<b>Historical Control Trials (HCTs)</b>	No Randomization, comparative studies with two or more treatments. These trials are conducted by comparing case histories and historical records.
<b>Observational Studies</b>	These studies may be of several types including the following: cohort, case-control or cross sectional design.
<b>Randomized Control Trials (RCTs)</b>	Oftentimes termed experimental study. These trials must be randomized.
<b>Active Control Trials (ACTs)</b>	Randomized, comparative studies of two or more treatment options. There is no placebo control.
<b>Placebo Control Trials (PCTs)</b>	Randomized, blinded with a therapy compared to a placebo control group. Patients are randomly assigned to either the experimental treatment arm or the placebo arm of the study. These types of trials may include double or triple blinding; they may also have multiple treatment arms. This is the type of trial that the FDA actually endorses and requires.
<b>Pre-Randomized Control Trials (pre-RCT)</b>	Subjects are placed into one treatment arm and then asked to consent to the therapy. There is no blinding, because patients in that are randomized to the standard treatment arm are not told there is an alternative, experimental treatment. Patients randomized to the experimental treatment are told it is experimental and asked to sign an informed consent agreement. In some cases patients receiving the standard treatment are not asked for Informed Consent. Proposed and defended by Zelen. <sup>28 29</sup>

In order to justify the claim for the epistemic necessity of Randomized Control Trials, it is helpful to examine the differences between several common

experimental designs. By examining a number of the standard clinical and non-clinical design methodologies, their relevant epistemic merits and defects, will be made apparent. It will be argued that randomized trials are epistemically superior to observational studies and that they are necessary in most cases to answer questions regarding the efficacy of medical interventions.

### **Analysis of Historical Control Trials**

In a Historical Control Trial, HCT, there is no randomization, no blinding, and no control. Given that these trials lack these elements, they will be open to many of the skeptical objections that were considered earlier. These trials are often termed “observational studies” but the use of this terminology can lead to confusion. The term is confusing because there is an equivocation in its use. The term “Historical Control Trial” is often used to refer to any number of diverse observational designs. As a stipulative definition, I will employ the term Historical Control Trial, HCT, to refer to those trials that are comparative studies that are conducted by examining historical patient records in order to collect data that in turn will be used to evaluate the effectiveness of a medical or psychological intervention. The data are collected by first defining a class of patients with particular features, and then examining the results when a medical intervention was employed. “In a clinical trial using historical controls, control data are derived from the experience of the institution with treatment of the disease in question accumulated before the introduction of a new therapy.”<sup>30</sup>

### **Three Types of Observational Studies**

The considerations mentioned above can be applied to other types of observational studies. Once again this is because there is no randomization, no blinding, and no control. Given that these trials lack these elements, they will be open to many of the skeptical objections that were considered earlier. I will examine three different types. These observational studies vary in significant ways depending upon the experimental methodologies employed.<sup>31</sup> In the hopes of clarifying the differences, I will mention the following types of observational studies that are uniquely different from HCTs: cohort design, case-control design and cross sectional design.<sup>32</sup>

In a cohort design trial patients/ subject are diagnosed and then the progression of their treatment/ illness is followed forward in time.<sup>33</sup> Physicians in this type of study will inform the patients of specific medical interventions and will note how each patient responded to the treatment.

In a case-controlled design, the first step is to identify cases with an outcome of interest. Once a number of cases have been found, the investigator selects controls from the source population. There are a number of methods for doing this, but regardless of the method, the level of exposure is compared between the cases and the controls.<sup>34</sup>

Finally, cases with a cross sectional design, which are sometimes referred to as prevalence studies, analyze both the exposure and outcome simultaneously. Prevalence rates are compared between the two groups; where exposure refers to an illness or disease and outcome refers to the end result of the progression of the

disease, i.e. death, or paralysis.<sup>35</sup> Each of these types of studies has certain epistemological defects. The main problem with each study is bias. This type of study design allows for the possibility of bias that will lead to inaccurate data. In other words, the researcher is examining patient records to determine to see if a particular medical intervention “worked” for a particular patient. This type of clinical study is open to several epistemic objections as will be discussed below.

### **Epistemic Concerns with Observational Studies and HCTs**

There are numerous and serious epistemological problems with this type of study. The first problem I will consider is the accuracy of the data collected. HCTs are conducted by reviewing patient charts. There is always the possibility that the charts under review contain factual errors. This is a possibility in any study, it is a type of information bias, but given the lack of rigor that may be employed in some settings, it would seem reasonable to conclude that the problem would be exacerbated in HCTs. These errors in turn lead to erroneous, misleading, or false data. Another issue is the possibility that the patients under consideration were misdiagnosed. These are both possibilities in any trial, but it would seem reasonable to conclude that this problem would be exacerbated in a situation where a researcher is considering records from a myriad of settings such as, hospitals, emergency rooms, trauma centers, private offices, and clinics. Each of these settings can provide challenges to the accurate diagnosis and treatment of a disease. Physicians working in an emergency room might overlook what may be essential features of a patient in their haste to save their life. Their primary function at that time is to act as a physician, not as a clinical researcher. They

should not be examining the patient in minutia, unless it is pertinent to the treatment and/or diagnosis. The same point holds for many other clinical care settings.

To consider this point further, in a RCT there are often rigorously, controlled conditions. Important data is often recorded immediately. The persons involved are engaged in a research activity- this may lead to great attention to detail. HCTs are conducted by review patient charts. For example, my physician is not one to record copious amounts of information. His notes are sketchy- at best. Employing his charts in a HCT may lead to inaccurate or incomplete data. This is much less likely to occur in a RCT given that they are often conducted in a research setting, with the intent of furthering medical knowledge.

In reality, most patients are lucky to have two minutes with their doctor on a routine office visit. The visit is often rushed, and the time and care given is cursory and incomplete. In some cases, due to the circumstances, the quality of care is not the best. As such we ought to be skeptical of the accuracy of the data collected in these environments. Using the data collected in such a situation in order to make a comparative study of disease and interventions remains suspect.

It is common knowledge that medical records are not uniform. Although they should be similar, they may not be the same. Each doctor or nurse is going to employ his or her own judgment in assessing and diagnosing patients. Further, not all of these professionals have the same background, education, training, or experience. In most cases the researcher had no direct interaction with the patient, and he may not be acquainted with the facility or the doctors involved. Given this

the researcher has no way of knowing the quality of the care provided or the quality of their records. Beyond this, recording information on a chart is not the same as recording information for a trial. The physicians involved may not exercise the same level of care, precision in their diagnosis, or exactness in their record keeping.

Importantly, even if we grant that all of the patients under consideration had the illness, there is no reason to conclude that all of the patients were at the same stage of the illness. It might be the case that the stage of progression of their illness is not recorded on the chart. If a researcher does not know, or cannot determine, at what stage of progression an illness was when an intervention was given, it will be impossible to determine with any great accuracy the efficacy of the treatment or intervention.

Let us imagine that a researcher does not know the stage of the illness, but is able to determine that a given patient had the disease under consideration; further that the researcher is able to determine that the disease appears to have been cured. It might seem reasonable to conclude that the treatment was efficacious in curing the disease. The researcher would no doubt take that as evidence in favor of the intervention. (For the sake of argument, let us assume that the disease did not go into spontaneous remission, or was somehow cured as the result of a placebo effect. Both of these are important considerations, but we must leave them to a side for a moment if we are to make any headway with our current example.) It might be the case that the intervention under consideration is able to

cure the disease in an early stage of progression, but not able to cure it in a later or end stage.

To consider the reverse, the intervention under consideration may not have any efficacy in the beginning of the illness but later becomes effective. If the stage of the disease is not noted on the chart, then a researcher might conclude what may be efficacious treatment at an early stage of disease does not work. To count all apparent examples of the efficacy or inefficacy of an intervention as equal in a historical control trial seems unjustifiable, unless the researcher can be reasonably certain as to the state of the patient and the stage of the disease.

To give a contemporary example, perhaps researchers are going to employ a historical study to examine the efficacy of certain interventions against breast cancer. Perhaps they come across a record for Elizabeth Edwards. Upon examination of her charts they note that a combination of chemotherapy and radiation therapy ultimately proved ineffective in treating her cancer. Is this evidence against the use of chemotherapy and radiation therapy? Let us assume that her doctors did not note in her records that she was diagnosed with metastatic or stage 4 cancer, which is not curable. Perhaps the fact that the stage of the cancer was not noted on the chart could result in the exclusion of her record from the trial. Yet even this omission opens the door for bias. It allows for bias because only patients whose doctors noted the stage of the illness will be represented in the study. As such, this is not a random sample and allows for selection bias.

Given the myriad of defects present in such trials it should be clear that they should be given limited epistemic weight. Trials of this type are not uniform; interventions were not employed in a controlled setting, the patient pool was not uniform, and the records may be inaccurate or incomplete. Again HCTs are conducted by examining the records of countless doctors, across institutions. With all of this in mind, it ought to be clear that any evidence collected from such a comparison is of the lowest grade. I argue that it is of the lowest grade; even if we restrict the inclusion criterion to employ patient records to those that are well documented. By restricting the inclusion to patients that are well documented I mean that we will accept as data for our comparison only those records to those where we have a well founded diagnosis that is consistent with clearly defined symptoms, as well as a clearly defined stage of illness. Yet as noted above, this will result in a type of selection bias.

Even if we could agree that all of the patients of such a comparison had the same illness, and were at the same stage of illness, and were prescribed the same intervention, there is no way to know how many patients actually followed the prescribed treatment guidelines of interventions properly. When patients leave the clinical setting, how are we to determine if they implemented the intervention under consideration? Should we take them at their word? Conduct an exit survey?

To illustrate, consider the following example: My doctor regularly prescribes medication for allergies and what he has termed, “reactive airways”. My chart says I take an allergy medication, a nasal spray, a once daily inhaler and a fast



acting inhaler on occasion. A thorough examination of my chart shows I have been suffering from this condition for two years. According to my chart I have shown no improvement. In fact, I have been prescribed at least three different types of medications for each of these symptoms. If a researcher were conducting a historical study that included my records, shouldn't he conclude that none of the drugs I had been prescribed was effective in treating my condition?

The truth of the matter is that, I never take any of those medications for more than a couple of days. After I see my doctor, I might take the interventions, specifically pharmaceutical products, on occasion but only when I am extremely troubled by my symptoms. In fact, I might lie and tell my doctor I take these drugs religiously, according to his prescribed guidelines, but that my symptoms never seem to improve. Certainly he must record this information on my chart.

What this case illustrates is that we ought to be wary of the data collected from even the very best historical trial. Patients are prone to "misinform" their doctors, and some doctors are careless in their record keeping. To put it simply, just examining a patient's chart is not going to provide enough information to know if the intervention under consideration was effective or ineffective. If we are to confirm or disconfirm the efficacy of a medical intervention we must employ a more reliable method of clinical study. These considerations ought to be sufficient to call into questions historical trials of this design.

Even if we grant that all of the patients are equal there will still be questions regarding the data collected. By saying the patients are equal, I mean that they all have the disease in question and the disease is at the same stage of progression.

Further we can grant that the medical interventions are given according to the prescribed guidelines, that none of the patients lied, or in any other way purposely deceived their doctors. As such, we can maintain that the study under consideration is an ideal historical control trial.

Yet even an ideal historical control trial is still open to skeptical challenge. The observed result can still be the result of confounding either from other unknown factors or variables, a placebo effect, or even spontaneous remission. These sorts of trials do not seem like a reliable procedure for collecting data, data that will be employed to draw an inference regarding the efficacy of a medical intervention.

### **The Epistemic Value of RCTs**

The epistemic value of Randomized Control Trials and their superior quality is endorsed by the World Medical Association (WMA), the United States Food and Drug Administration (FDA), and many researchers in the evidence based medical movement. This alone does not show that RCTs are, in fact, superior, nor does it show that they are even necessary. Further, it will be argued that not all RCTs are equal- some RCTs are better than others for various reasons.

Although the WMA and the FDA have endorsed RCTs, it is certainly possible that these organizations are mistaken. In fact many physicians and researchers who are also members of these organizations deny the assertion that RCTs are epistemically necessary. In other words, the question of the epistemic need is not settled. It is my intention to argue that experiments that include randomization, double blinding, placebo control (a placebo control group) are all necessary in

most cases to establish the efficacy of a treatment. It might be the case that RCTs are not necessary in all situations to establish the efficacy of a treatment or medical intervention. There might be certain rare cases, such as the introduction of penicillin, where RCTs are not necessary to establish efficacy, but, generally, they are necessary.

I claim that RCTs provide a higher quality of evidence than other types of clinical research design. The quality of the data obtained from a well run RCT is far superior to that which could be obtained by other types of experimental designs. RCTs provide data that avoids several types of bias that are endemic in other experimental designs. Given that RCTs can avoid, in principle, several types of bias that other types of study design cannot, the data collected is potentially of a higher quality. Observational studies are unable to avoid several types of bias. It will further be demonstrated that observational studies are unable to answer the skeptical challenge raised by the placebo effect. RCTs can avoid most types of bias and can answer many skeptical objections; as such data collected in a RCT ought to be given a greater weight for or against the medical and or psychological intervention under consideration.

If RCTs were not employed there would be a number of skeptical objections that could be raised regarding the evidence obtained from other experimental designs. This would severely hinder the ability of clinical researchers and physicians to confirm the efficacy or effectiveness of certain medical and or psychological interventions. In fact, as has been argued, in most cases one could not confirm the efficacy of an intervention without employing a RCT.

When considered epistemically, I argue that RCTs are necessary to confirm or disconfirm the efficacy of most therapies. As was illustrated above, RCTs avoid a variety of skeptical objections that cannot be avoided by most other types of experimental methodologies. RCTs are necessary because they can avoid several different types of bias, which can distort data collected under other types of experimental designs.

An analysis of alternatives to RCTs, particularly those that are sometimes termed “historical control trials” or “observational studies” shows that statistical bias emerges in the data. Statistical bias is endemic in the design methodology. Most statisticians are aware of this fact. For example, when they attempt to analyze the data collected under these design methodologies, they attempt to interpret the data in a way that will take into consideration the inherent bias found in the design methodology. RCTs avoid this bias in virtue of their design. It is not the case that RCTs can avoid all bias, (because of human error which is endemic to all forms of clinical research) yet RCTs are better able to avoid statistical bias than other clinical designs. If one argues that we must eliminate the potential for all bias before we make a claim of efficacy, then we will be left with the skeptical conclusion that it is impossible to confirm the efficacy of any medical intervention, and further that no past or current medical intervention has ever been confirmed. If certain interventions have been confirmed, then how has this been done? My answer is that it has been done by employing RCTs. If there is an alternative explanation, then the onus is upon my critics to articulate just

such an alternative. With these considerations in mind, RCTs can confirm efficacy, whereas in most cases other types of experimental design cannot.

### **Epistemic Analysis of Randomized Control Trials**

In Randomized Control Trials, RCTs, patients are randomly placed into one of the treatment arms. This process can be compared to a coin toss that is done by a computer. During clinical trials, no one likely knows which therapy is better, and randomization assures that treatment selection will be free of any preference a physician may have. Randomization increases the likelihood that the groups of people receiving the test drug or control are comparable at the start of the trial, enabling comparisons in health status between groups of patients who participated in the trial. This procedure can be employed in order to avoid, in theory, selection bias.

If all of the patients are receiving some form of treatment then they participating in an active control clinical trial, (ACT). In an ACT, patients are randomized into different treatments; thereby comparing one treatment against another. A number of these issues have been discussed in Erwin (2006)<sup>36 37</sup>. Erwin has argued that a placebo control is necessary in many cases because of the possibility that both the "best treatment" and the new treatment are ineffective. From this he argues that the skeptic can claim that you are simply testing one poor treatment against another, unless one of those treatments has been established as effective. In order to do this, it would seem that one of the treatments must have been tested against a placebo control group. If an intervention cannot outperform the placebo control group, then that would seem to disconfirm its efficacy. It

might be the case that an intervention could be tested against a standard therapy, if the standard therapy has been tested and outperformed a placebo control. As such, there should be some measure of transitivity between trials.

Another type of clinical trial is pre-Randomized Control Trials, (pre-RCT). In this type of trial, subjects are placed into one treatment arm, and then they are asked to consent to the therapy. Under this design there is no blinding.

(Technically this is an ACT without blinding.) In some cases patients receiving the standard treatment are not asked for informed consent. They are not told that they are participating in a clinical trial to study the efficacy of their treatment. This type of design was proposed and defended by Zelen.<sup>38</sup> Although this type of trial may be epistemically sound, I argue against it in chapter 3 on ethical grounds.

In a placebo control trial, PCT, patients are randomized and blinded. When they are blinded they are not told what type of therapy they are going to receive. In this type of study a therapeutic treatment group is compared to a placebo control group. Patients are randomly assigned to either the experimental treatment arm or the placebo arm of the study. These types of trials may include double or triple blinding; they may also have multiple treatment arms. In a Randomized Control Trial with a placebo control, test subjects sign an informed consent agreement before they are placed into a particular arm of the study. What the subjects are told regarding their treatment depends upon a number of factors.

Once again, randomization is necessary to eliminate the possibility of selection bias. In conjunction with randomization, a feature known as "blinding" helps

ensure that bias doesn't distort the conduct of a trial or the interpretation of its results. Single-blinding means the participant does not know whether he or she is receiving the experimental drug, an established treatment for that disease, or a placebo. In a single-blinded trial, the research team does know what the participant is receiving.

A double-blind trial means that neither the participant nor the research team knows during the trial which participants receive the experimental drug. Triple blinding means that no one including the physician, the patient, or the statistician knows who received the active substance and who received the placebo. The patient will usually find out what he or she received at a pre-specified time in the trial. Controlled conditions are necessary to establish a causal relationship between the proposed intervention and the effect on a patient. Without conducting an experiment in a controlled setting, the skeptic can rightly challenge the efficacy of the treatment because they cannot be certain that some unknown variable was the cause for the patient's improvement. Finally, because of the placebo effect, a placebo control group is necessary in order to confirm the efficacy of an intervention. A control group can rule out the possibility of spontaneous response, and having a placebo control group can rule out the possibility of patients having a placebo response to the intervention.

### **The Placebo**

The term was first defined in a medical setting in 1785 in the second edition of Motherby's New Medical Dictionary, as "a commonplace method or medicine."

<sup>39</sup> The definition was later expanded to say, "a commonplace medicine or

medicine calculated to amuse for a time, rather than for any other purpose.” (1795, 1801 Motherby); it was not until 1951 that the placebo was defined in medical dictionaries as an inactive or inert substance. This definition restricts the term placebo to substances, whereas the original definition allowed for the possibility of a placebogenic method; such as laying of hands, to cite one example.

Implicit in the early definitions of the placebo was the idea that the patient was pleased or amused by the treatment. This seems to indicate that, regardless of efficacy; a placebo may have a beneficial psychological effect or make them feel better. This psychological effect is known as the placebo effect. There has been much debate about the proper definition of the placebo. Arthur K. Shapiro has been writing on the subject since 1960. A placebo may be defined, as it is by Shapiro, “any treatment (including drugs, surgery, psychotherapy, and quack therapy) that is used for its ameliorative effect on a symptom or disease but that actually is ineffective or in not specifically effective for the condition being treated. The placebo effect, then, is primarily the nonspecific psychological or psycho physiological therapeutic effect produced by a placebo, but may be the effect of spontaneous improvement [or remission] attributed to the placebo.”<sup>40</sup>

The definition above has been honed by the criticism of many commentators on Shapiro’s work. Many shortcomings of earlier definitions of the placebo were elucidated by Adolf Grümbaum in his various books dealing with psychoanalysis. I will mention one problem with Shapiro’s current definitions of placebo and the placebo effect. In the definition stated above he assumes that the physician



knows that he is prescribing a placebo, but, as he is apt to point out, “the history of medicine is the history of the placebo”. As Grümbaum says, “While some placebos are known to be such by the dispensing physician- though presumably not by the patient- other placebo therapies are mistakenly believed to be nonplacebos by the physician as well.”<sup>41</sup>

For the better part of the history of medical, placebos have been prescribed unwittingly by physicians. There may be situations where a physician knowingly prescribes a procedure that he is aware will have no specific therapeutic action upon a disease, but there are many more times when the physician does so out of ignorance. For example a physician may prescribe a CAT scan to a patient suffering from cancer phobia knowing full well that the examination is unnecessary, but does so because he believes it will have a placebogenic effect upon the patient. In this case the physician is employing an effective diagnostic tool as a placebo in this situation for the benefit of the patient.

The example above is falls under condition (d) of Adolf Grümbaum’s definition of an intentional placebo. Adolf Grümbaum defines the placebo as follows:

A treatment process  $t$  characterized by a given therapeutic theory  $\Psi$  as having constituents  $F$ , but also possessing other, perhaps unspecified incidental constituents  $C$ , will be said to be an “intentional placebo” with respect to a target disorder  $D$ , suffered by a victim  $V$  and treated by a dispensing practitioner  $P$ , just when the following conditions are jointly satisfied: (a) none of the characteristic treatment factors  $F$  are remedial for  $D$ ; (b)  $P$  believes that the factors  $F$  indeed all fail to be remedial for  $D$ ; (c) but  $P$  also believes that- at least for a certain type of victim  $V$  of  $D$ -  $t$  is nonetheless therapeutic for  $D$  by virtue of containing some perhaps even unknown incidental factors  $C$  different from  $F$ ; and (d) yet- more often than not-  $P$  abets or at least acquiesces in  $V$ ’s belief that  $t$  has remedial efficacy for  $D$  by virtue of some constitutes that

belong to the set of characteristic factors  $F$  in  $t$ , provided that  $V$  is aware of these factors.<sup>42</sup>

Grümbaum's definition of the placebo is applicable to both medical as well as psychological interventions. He prefers the terminology "incidental" as opposed to "nonspecific" when discussing the features of an intervention that are placeboogenic in nature. On his view, if an intervention contained some elements that were placeboogenic, but other that were not, then the intervention could still be deemed effective. Although Grümbaum's definition of the placebo is applicable to a broad range of interventions, it is not without its problems. One issue is this: Grümbaum builds into the definition of placebo the notion that it is "harmless to the victims". I think that employing the term "victim" makes the assumption that placebos are somehow wrong or unethical. Further, it may be the case that the placebo itself is harmless, but that because a patient is receiving a placebo (and not treatment) he is harmed as a result of his condition. For example, if a sugar pill is used a placebo in a clinical trial testing a new intervention against cancer, the sugar pill is harmless, but the receiving of a sugar pill as opposed to a therapeutic intervention may result in death!

I think that Grümbaum may have intended an ethical component to this definition of the placebo, but, as stated, it is not sufficient. I think that ethical issues should be separated from epistemic issues; as such, we should define the placebo in such a way so that everyone involved in the discussion can agree as to what it is, and then proceed to consider whether or not the use of a placebo is ethical. I do not feel that the issue is resolved by incorporating ethical aspects into the definition of the placebo itself. I define the placebo as follows: any

treatment (i.e. device, drug, therapy) that has no specific therapeutic action upon a patient's condition but has the potential to produce a placeboogenic response.

Most ineffective treatments could meet this condition.

### **The Epistemic Necessity for a Placebo Control**

Given that some patients are drug responsive, the most obvious way to rule this out is by means of a placebo control group. As such it would seem that one necessary condition for establishing a treatment as effective treatment is that it has been tested against a placebo control in order to rule out the possibility of a placebo effect. Yet a placebo control does not, by itself, guarantee the accuracy of the data.

In light of his definition of the placebo noted above, Grümbaum defines a placebo control as follows:

A treatment type  $t$  functions as a “placebo control” in a given context of experimental inquiry, which is designed to evaluate the characteristic therapeutic efficacy of another modality  $t^*$  {by “modality” Grümbaum means medical intervention or treatment} for a target disorder  $D$ , just when the following requirements are jointly satisfied: (1)  $t$  is a generic placebo for  $D$ , as defined under the first condition (a) in the definition above of “intentional placebo”; (2) the experimental investigator conducting the stated controlled trial of  $t^*$  believes that  $t$  is not only a generic placebo for  $D$ , but also is generally quite harmless to those victims of  $D$  who have been chosen for the control group... With respect to the target disorder  $D$ , the treatment modality  $t$  belongs to the genus placebo just when its characteristic constituents fail to be remedial of  $D$ . Furthermore, clarity is served by using the term “incidental” rather than “nonspecific” when speaking of those treatment constituents that differ from characteristic ones.<sup>43</sup>

The same criticisms of Grümbaum's definition of the placebo hold for his notion of the placebo control group.

Several arguments have been given for a placebo control group. It seems to me that in most cases, in order to be established as an effective treatment, a placebo control is necessary. In part this is because there is a measurable placebo effect in almost all clinical research. Some patients improve simply because they receive a treatment- any treatment, even in ineffective one. A recent HIV clinical trial had a 35% improvement in the placebo control group.<sup>44</sup> The fact that patients improve in such a situation ought to highlight the need for a placebo control group. The only way to account for the placebo effect or cases of spontaneous remission is to employ a placebo control group. The FDA, correctly, endorses evidence obtained from “a properly randomized, controlled trial” as of the best.<sup>45</sup> When this view is fleshed out, the FDA means, that the participants of a “properly randomized, controlled trial,” are properly blinded, (in their view, this assures assay sensitivity) and at least one arm of the study contained a placebo control group. Many researchers seem to think that the conditions mentioned above are sufficient to guarantee accurate data.

Assay sensitivity is the notion that the clinical researcher must not bias the sample by allowing the subjects to know they are receiving a placebo. At the minimum this requires “blinding”. Blinding means that the researcher does not tell the subject what treatment he is receiving. If there is a placebo, he is not told that he is being given one. Some study designs involve double blinding, where the clinician that administers the treatments does not know which patients are receiving the placebo or in the placebo control group. Yet blinding alone does not assure that the data are not biased. Blinding may be a necessary condition of

avoiding statistical bias, but blinding alone is not sufficient to guarantee assay sensitivity.

Blinding is not sufficient to assure assay sensitivity for a number of reasons. One reason is that if a believable placebo is not employed in the trial it may cause subjects in the placebo control group to doubt the veracity and reliability of the placebo, hence tainting the data collected. Further, even if a believable placebo is employed, and the research subjects are properly blinded, the research team will know which subjects are receiving a placebo. Given this fact, there is always the possibility, inherent in any RCT that is single blinded that the researchers give away during the course of the investigation which subject are receiving the placebo.

One solution to this possibility is to employ double blinding in the experiment. When double blinding is employed, neither the physicians nor researchers that have interaction with the patients nor the patients know who is receiving the placebo and who is not. Theoretically, in this case, the researchers will not know, or be able to determine which patients are receiving a placebo. As such, it would seem that they are not in a position to bias the data by letting the patients know if they are receiving a placebo or not. Yet, even in this case, when double blinding is employed, and done correctly, the researcher will often be able to determine which research subjects are receiving the placebo and which are not during the course of the trial as they collect data from the subjects. As such, assay sensitivity is not guaranteed even in a properly double blinded trial. This has led some commentators to argue for the use of “placebos” that simulate the effects of

the medical intervention under consideration. If a “placebo” is simulating effects, then it is no longer a placebo- it is an active substance. I think that what some of these people have in mind is the use of an active control trial, as opposed to a placebo control trial. The reality is that some patients will have a reaction to the medical intervention, even when given an inactive substance. Again, that is the rationale for employing a placebo control. It seems as though they have missed the point of the placebo control.

Studies with a double blind design methodology may be able to answer the skeptical challenge that the clinical investigator inadvertently allows the research subject to know that he is receiving a placebo. If the subject knows that he is receiving a placebo then this will reduce or eliminate his expectation of an efficacious result for the treatment. By lowering the participants’ expectations for the success of the treatment, the data collected may be biased. The research subject expects the treatment to fail, this will most likely result in inaccurate data. If he expects it to succeed, this may lead to a positive assessment of the treatment. Again it is claimed that a placebo control is needed to rule out bias of this type.

Placebos of various types including; inert substances, dummy pills, sugar pills and sham surgeries, have been employed in numerous research studies and trials. In nearly every case where placebos have been employed there have been patients that have responded to these treatments. Although patients respond to the treatment, there is no physiological reason or scientific basis for these people to improve. Given that patients may respond to such a treatment, then it is epistemically necessary to be able to differentiate a placebo response from an

efficacious one. This can be accomplished by establishing a baseline reading to show that the medical or psychological intervention under consideration actually works. If the treatment cannot outperform a placebo control group, then I would argue that the experiment has failed to confirm the efficacy of the treatment.

Again I make this claim based on the fact that, for any given group of patients with a certain condition, an indeterminate number of patients will respond to any intervention- even a placebo. As such, the central reason to employ a placebo control is to rule out the possibility that research subjects have responded to an ineffective treatment. Just giving the patients a treatment and asking them if they improve is not sufficient to establish efficacy. It is not enough to simply ask for their feed back or record their responses as they may improve as a result of the placebo effect.

There is documented evidence that patients “feel better” (find a treatment to be efficacious) simply because they think it will work. The central epistemic difference between observational studies and RCTs is that RCTs (with a placebo control), if run correctly, can account for the placebo effect, whereas observational studies, no matter how well they are run, cannot. No observational study, in principle or practice, can account for the placebo effect. This is the fatal flaw of observational studies, one that will support my thesis that RCTs, (with a placebo control), are epistemically necessary to confirm the efficacy of most medical and or psychological interventions.

To cite one of the numerous examples, in a recent study volunteers were shocked by an electrode hooked up to their wrist. A short, painful burst of

electricity was sent through the electrode. The volunteers were then given a placebo cream to rub on their wrist and then they were told the cream had analgesic effects. The volunteers were then shocked again. Over 50% of the volunteers said that the pain was less or negligible as compared to the first shock.

Although there is a great deal of evidence in support of the existence of the placebo effect, its significance is often misunderstood or ignored. The importance of a placebo control cannot be overstated in clinical research, yet many researchers often dismiss its significance. Many of the arguments against the placebo control are not epistemological but rather ethical in nature. The following is an example meant to exemplify this point. This is a quote taken from an anthology entitled, “Ethical and Regulatory Aspects of Clinical Research”. In the article, “The Continuing Unethical Use of Placebo Controls”, Rothman and Michels argue that, “No scientific principle, however, requires the comparison in a trial to involve a placebo instead of, or in addition to, an active treatment.”<sup>46</sup> Many of their arguments conflate issues of ethics with issues of scientific rationale and/or epistemic justification. Rothman and Michels examine three “epistemic arguments” that are advanced in support of placebo controls, yet, in their views, “none of which withstands scrutiny.”<sup>47</sup>

They state the first argument as follows: “By allowing investigators to determine whether a new treatment is better than nothing (beyond the psychological benefits of treatment), a placebo control offers a clear benchmark.”<sup>48</sup> In fact, it can be added that unless a placebo control is employed, the skeptic can rightly maintain that you may be comparing one ineffective



treatment to another. This point has been made by several others including Temple and Ellenberg (2000) as well as Erwin, (2006).

To quote from Erwin:

...if no placebo control is included, and a new drug does approximately the same as a standard treatment, one cannot infer that the new drug was effective unless one makes another assumption: that the standard treatment was effective in that particular study. Support for that assumption must come from sources external to the trial; for many drugs, there will be no such evidence. To put the point another way, in a best treatment comparison where the outcomes are roughly the same, to infer that both were effective, we need to assume that in this particular study, had a placebo group been included, the placebo would have been inferior to the standard treatment. Without the inclusion of a placebo control, there is often no way to tell if this assumption is true.<sup>49</sup>

As is pointed out above, even when there is an established “standard treatment”, and the new intervention out performs the standard treatment, one must assume that both the standard treatment and new intervention would out perform a placebo control. It might be the case that one ineffective treatment is being compared with another. Rothman and Michels ignore this concern, and discount this argument by citing what they consider to be an authoritative source, A. Branford Hill, “Is it ethical to use a placebo? The answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proven or accepted value. If there is such an orthodox treatment the question will hardly arise, for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing at all.” Again, this assumes that the orthodox treatment has, in fact, been proven to be effective. I will concede that if the orthodox treatment has been clinically proven to outperform the placebo, then one may be able to employ an active control trial, comparing the

new treatment against the orthodox one. In many cases the standard or orthodox treatments have not been compared to a placebo control, as such, there is still a need to employ a placebo control in order to establish efficacy.

Returning to Rothman and Michels' argument against the epistemic need of RCTs, simply citing Hill's view is to commit the fallacy of appeal to authority. Further, in the case of Hill, he was considering the ethical concerns in the use of a placebo, not the epistemic concerns. Regardless of the context, it is an error to think that citing Hill's view is sufficient to discount the use of placebo controls.

The second defense of placebo controls that Rothman and Michels consider is that determining which treatment is actually better than another is, in their words, "not always a straightforward matter." They point out, rightly, that beyond efficacy there can be other factors such as, "interactions, costs, routes of administration and other factors." Nevertheless these "other factors" have no bearing on the epistemic question of whether a treatment is efficacious. Rothman and Michels have conflated epistemic concerns with ethical, economic, and pragmatic concerns. It appears to be their view that some researchers would rather assign a placebo than determine which standard treatment is the best, all things considered. I am not sure if this is the case. Even if this were the case, in a situation where there is no clear "standard treatment", it does not seem that there is an epistemic reason why research subjects must be assigned to a standard therapy, especially since this would be impossible. Finally, Rothman and Michels again conflate the ethical and epistemic issues when they say, "It is not justifiable, however, to assign placebo controls simply to avoid the complex decision of

which treatment should be used as a standard. Investigators are ethically obliged to make such decisions.”<sup>50</sup> This last sentence of the quote may be a reference to clinical equipoise. The ethical consideration of assigning research subjects to a placebo control arm will be considered in subsequent chapters. At present, the issue is whether there exist compelling epistemic reasons or concerns for their use. As, I have said, I argue that there are compelling epistemic reasons for employing placebo control trials.

The final argument presented by Rothman and Michels against placebo controls involves statistical significance. The authors argue that by comparing new treatments against placebos, statistical significance is skewed in favor of the new treatments in a misleading way. According to the authors:

The significance of an association depends upon two characteristics- the strength of the association and its statistical variability. A weak effect can be “significant” if there is little statistical variability in the measurement, whereas a strong effect may not be “significant” if there substantial variability in the measurement... Ideally, statistical variability should be reduced nearly to zero when the magnitude of a drug effect is assessed, so that random error does not influence assessment. Unfortunately, the main way to reduce statistical variability is to conduct large studies, which are expensive. Statistical significance, on the other hand, can be obtained even in small studies, if the effect estimate is strong enough. When a placebo is used instead of an effective treatment, the effect of a new drug appears large and may be statistically significant even in a small study. The scientific benefit, however, is illusory. Because the study is small, the measurement of the effect is subject to considerable statistical error. Thus, the actual size of the effect, even when a new drug is compared with placebo, remains obscure, and the study does not address the effectiveness of the new treatment as compared with currently accepted treatments.<sup>51</sup>

This argument involves several issues. First, let us assume that Rothman and Michels are correct in their description of statistical significance, then so long as

statistical significance can be achieved in a study, it should not matter if the study is large or small. It has long been claimed that larger studies are better than smaller studies, but this is not necessarily the case. In fact, recent statistical research has demonstrated this to be false.<sup>52</sup> Smaller studies can have just as much statistical power as larger studies. Rothman and Michels claim that it is not possible to establish efficacy with a small study if the study involves the comparison of the new intervention against an active treatment. They claim that researchers are stacking the deck in their favor by employing a placebo control as opposed to an active control. To claim that the efficacy is “illusionary” in a small study is simply wrong. This is a mistake, one that demonstrates that they do not understand the epistemological importance of a placebo control.

Bacchetti et al. argue that smaller studies can provide just as much “power” as larger studies. If a treatment is given to seven patients in controlled conditions, and all seven improve, surely we have evidence of efficacy. The exact number of test subjects necessary to establish efficacy may vary from case to case. There has been a great deal of debate about sample size in clinical trials. Some, such as James Wright, have argued for large mega trials to confirm efficacy; whereas Michal Pijak argues for smaller trials.<sup>53 54</sup>

In general, I have concerns regarding the number of test subjects involved in establishing efficacy. The FDA approval process has several goals, one it to establish efficacy, another is to ascertain side effects. I feel that smaller trials, with a limited number of test subjects, allow potentially dangerous treatments to be approved. The vast number of treatments that have been taken out of the

market, after initially being approved by the FDA, highlights this problem. Nevertheless, questions of efficacy and side effects of a new treatment are separate issues. It may be the case, as Bacchetti claims, that small studies can be used to establish efficacy, but that larger studies are needed to determine side effects.

At this juncture, we are examining the question of how to best establish the efficacy of a treatment. A treatment may be efficacious, and yet have severe side effects. It might be the case that the side effects may not come to fruition until after months or years of continuous use. In such a case, they would not be discovered under the current FDA system, even if the number of test subjects were dramatically increased. There will always be dangers when testing new treatments. The epistemic goal of establishing efficacy may often conflict with ethical concerns, but those concerns should not be conflated with epistemic ones.

Returning to the criticism of Rothman and Michels, they claim that a new treatment must be compared with the standard treatment in order to establish efficacy. I would claim that they are mistaken; it is not necessary to compare a new treatment against the standard therapy. It is entirely acceptable to compare a new therapy to a placebo control. Furthermore if a new treatment were not any more effective than the placebo, then it would not be possible to establish any statistical significance difference between the new therapy and the placebo. To argue that the statistical significance is illusory is to beg the question against placebo control trials. The same could be true of active control trials involving the standard treatment. Many authors, such as Rothman and Michels argue that

comparing a new therapy against a placebo, stacks the deck in the favor of the new therapy. They claim that because you are testing a new treatment against now treatment, it is easier to claim efficacy for the new treatment. This is a mistake. If a new treatment outperforms a placebo, then it is efficacious in treating the target disease. If it fails to outperform the placebo control then it is not effective; in other words it has been disconfirmed.

One legitimate point that may be raised in this situation is that the new therapy may be more effective than a placebo, but less effective than the standard therapy. As a result of a placebo control trial you may not be able to compare the effectiveness of the new treatment with the standard treatment. Nevertheless, this inability to compare the new treatment with the standard treatment has nothing to do with the efficacy of the new treatment. If a placebo control trial is employed, then there is no measure with which to compare the new therapy against the standard therapy unless both were compared to the placebo.

If the standard treatment had previously been compared to a placebo, then the data could, in principle, be used to draw a comparison between the two. One solution to this problem is to employ a multiple arm trial where some experimental subjects receive a placebo, others receive the standard therapy, and others still receive the new therapy. There is no reason why a multiple arm study could not be run in which a placebo, new drug, and standard treatment were all compared. In this case, one could establish the efficacy of both the standard and new treatments, and at the same time, determine which treatment is superior.

### **Philosophical Examination of Meta-analysis**

Although it has been argued that Randomized Control Trials, RCTs, are superior to other experimental methodologies, there is new evidence supporting the results of other types of studies. Several researchers have conducted comparative meta-analyses of the finding of RCTs as compared with observational studies of the same clinical topic and found the results of observational studies to be more precise than the results of RCTs.<sup>55</sup> In a meta-analysis, data are taken from various diverse studies, (some which may have been conducted under different experimental methodologies) in order to draw an inference from the complete data set. At best, the results of these studies provide some evidence that other types of experimental designs can produce data similar in quality to that attained from RCTs<sup>56 57 58</sup>. Yet this evidence is not above reproach. As has already been argued other experimental methodologies suffer from epistemic flaws which in most cases open them to skeptical objection. Nevertheless since numerous researchers are calling into question the necessity of RCTs on the basis of these studies, they should be examined. When these studies are considered it will be demonstrated that there are several epistemic difficulties that are encountered when conducting a meta-analysis.

In a meta analysis conducted by Benson et al. (2000) 136 studies involving 19 diverse treatments were compared. Their analysis of the data showed that “in only 2 of the 19 analyses of treatment effects did the combined magnitude of the effect in observational studies lie outside the 95% confidence interval for the combined magnitude in randomized, controlled trials.”<sup>59</sup> From this they

conclude that there is “little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained by randomized, controlled trials.”<sup>60</sup>

An obvious objection to the criticism is that pooling the data collected from diverse trials conducted under different conditions is inherently biased unless it can be established, empirically, that all of the trials were of similar quality. It might be the case that what are being compared are very good, well conducted observational studies, and very bad, poorly run RCTs. If that is the case, then observational studies might seem equal, if not superior to RCTs.

Further, even if we were to grant that the studies under consideration are of similar quality, there are various ways that RCTs and observational studies may be compared. RCTs and observational studies of the same medical intervention can be compared, or RCTs and observational studies of various diverse interventions and conditions can be compared. The Benson analysis mentioned above pooled all studies of a particular type together. It compared the data from all RCTs, regardless of the quality, and regardless of the medical intervention under consideration. It also compared all of the data, regardless of the quality, and regardless of the medical intervention under consideration for observational studies. This is yet another reason to question the validity of their conclusions. It seems unfair to assume that different RCTs studying the same intervention are homogeneous, let alone every RCT they could get their hands on. The same criticism applies to the observational studies under consideration. Why assume they were all conducted in the same manner?



Comparing data from two RCTs, even when it involves a comparison of the same medical intervention may show a wide divergence in the data. One way to explain this divergence, or lack of precision, is that one of the trials was of a lesser quality than the other. To sound cliché, it's like comparing apples to oranges. This criticism is only magnified when you are comparing multiple RCTs, involving various medical interventions. In point of fact, an analysis of the studies under consideration of Benson et al. shows just this. The wide range of data collected, by RCTs and observational studies regarding the same medical condition and/or intervention ought to set up a red flag. It seems clear that there were importance differences, either in the methods, procedures, or in patient populations (to name just a few possible explanations) that ought to make one wary of considering all of these studies in a meta-analysis. The wide disparity in data seems to show that not all RCTs are equal.

One problem with the pooling of data collected from many diverse trials is that they are conducted under different conditions. Given this fact, the data being compared may be of varying quality. These trials may have different inclusion/exclusion criteria; as such they may have different study significantly different study populations. All of these factors seem to be inherently biased. Meta analysis involves comparing apples to oranges and then assuming that they are all apples. Even if we were to assume they are all apples, there may be one or two bad apples in the bunch (say a poorly run RCT) that skew the results of the meta- analysis. Unless these differences are accounted for, it is unclear how reliable meta-analysis can be. How are we to know that all of the RCTs we are

employing for our meta-analysis are of similar quality? Why should we consider all of the data as being of equivalent merit or value? Another problem is how the data are to be interpreted. There are two common methods of interpreting data according to statistical theory. One is the Neaman-Pearson method, the other is a Bayesian method. These two methods give divergent interpretations as to what counts as data. This is important because the same data, collected by a given clinical trial, depending upon the statistical method employed can lead the researcher to draw different conclusions.

In principle most of these issues can be overcome. One day meta-analysis could be a useful tool for comparing the reliability of data collected under diverse experimental designs; unfortunately that day is not today. At present, it is unclear how reliable the current set of meta-analyses are in comparing RCTs to observational studies. Further, the process and procedures employed in meta-analysis are not uniform. Given this lack of uniformity the current results of meta-analyses are all open to epistemic challenge.

A final issue to consider when discussing meta-analysis is publication bias. Meta-analyses are conducted by examining the published results of clinical research. If researchers are comparing published studies, it is possible that not all types of studies are published. It is certainly the case that particular journals may favor studies of a certain type over another. This may bias the pool of evidence that will be considered in a given meta-analysis. To claim that observational studies are now equal to RCTs is to ignore thousands of years of evidence to the

contrary. As stated in the outset, RCTs have been of central importance in moving medicine from an imprecise art to a very accurate science.

### **Epistemic Conclusion**

According to the FDA, “The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.”<sup>61</sup> The FDA holds that RCTs are the optimal research methodology for conducting clinical investigations; this view has been challenged on epistemological grounds. I have endeavored to support this view by pointing out epistemic weaknesses in other types of clinical trials.

The main epistemological objection to RCTs is that they are unnecessary because the efficacy of these treatments can be established by means of other types of experimental methodologies or even non-experimental methodologies. As I have tried to illustrate above, observational studies open the possibility for error in many ways. Another way to put this is as follows: I would argue that other types of designs cannot answer the required epistemological questions for a wide range of medical and psychological interventions because they are open to skeptical objection; as such there are certain epistemic questions that can only be answered by RCTs. Specifically, there are certain features of RCTs that make the quality of data collected superior to other experimental methodologies. As was stated in a recent editorial in the *New England Journal of Medicine*:

All observational studies have one crucial deficiency: the design is not an experimental one. Each patient’s treatment is deliberately chosen rather than randomly assigned, so there is an unavoidable risk of selection bias and of systematic differences in

outcomes that are not due to the treatment itself. Although in data analysis one can adjust for identifiable differences, it is impossible to be certain that such adjustments are adequate of whether one has documented all the relevant characteristics of the patients. Only randomized treatment assignment can provide a reliable unbiased estimate of treatment effects.<sup>62</sup>

In their words, embracing more observational studies would lead to “considerable dangers to clinical research and even to the well-being of patients”. The central purpose of this first chapter is to defend the epistemic necessity of RCTs. The essential features are randomization and placebo control. Randomization is necessary to, at least in principle, rule out selection bias. Selection bias results when a clinical researcher selects test subjects that are more likely to respond to the intervention under consideration, perhaps in an effort to bolster the positive results of the intervention. Such bias would call into question the validity of the data collected in the trial. This feature, along with double blinding, and a believable placebo are necessary to rule out a number of skeptical challenges that can be raised under other experimental methodologies.

## **Chapter 2: The Right to Enroll in Clinical Trials: Autonomy and Informed Consent**

There are several ethical objections and concerns raised to clinical research. Most of the objections are aimed specifically at Randomized Control Trials, yet other types of trials are also argued to be ethically objectionable or impermissible if they are conducted using certain “vulnerable” populations such as the poor. I claim that many of these objections are, at their heart, paternalistic in nature. Instead of respecting the right of persons to engage in activities of their own choosing, critics of RCTs and PCTs want to protect people from themselves. I argue against the insidious notion of paternalism that has seeped into the discussion of the ethical permissibility of clinical trials. I characterize it as insidious, because few authors argue (or admit) that they are supporting a species of paternalism. Many authors aim to protect patients/ experimental subjects from the risk inherently found in clinical research at the expense of their basic rights. In doing so they violate, at a minimum, one basic right of competent adults: the right of self determination, i.e. the right of competent adults to determine for themselves their own choice of goals and ends in accordance with their values.

In my view we must move from a paradigm of protection of rights to one of respect for rights. Researchers and ethicists need not protect experimental subjects from themselves. A transition in thinking ought to take place in this area. We should move from evaluating the ethics of clinical research from the perspective of protection towards judging it from the perspective of respect. The paramount ethical concern ought to be the rights and individual autonomy of the

research subject. I defend most clinical trials as ethically permissible so long as the rights of the experimental subjects are not violated. Clinical studies ought to be structured and conducted so that they do not violate the rights of the research subjects and respect their capacity to exercise their individual liberty. In general I feel that ethical considerations take precedent over epistemic ones.

Both doctors and clinical researchers have specific obligations to their patients and to their research subjects respectively. When asking a patient to participate in a clinical trial they must warn the patient of the risk involved. The researcher must explain that there is a level of uncertainty when it comes to the suspected outcome of the clinical trial. At times there is great uncertainty regarding how a purposed medical intervention will affect the experimental subject. Finally they must obtain the patient's informed consent to be used as an experimental subject. Basically the physician has an obligation to make sure that the experimental subject understands what he is getting into. If those obligations are not met, if the rights of the experimental subject are not respected, then a clinical trial is not ethically permissible.

There is currently a shift in the practice of medicine from paternalism towards individualism. In the past the physician may have had *carte blanche* to suggest (require or, perhaps, demand) a course of treatment now, often times, he allows the patient to choose among various treatment options. The current paradigm in medicine is for the doctor to provide the patient with the necessary information about different treatments, but then allow the patient to have (in many cases) the final say regarding his therapeutic options. This view is at odds with the

paternalism of the past, where the doctor usually had the final word regarding the patient's care. A similar shift in thinking ought to take place in the realm of clinical research. The paternalism of the past ought to be abandoned in favor of an enlightened respect for experimental subject's rights. The ethical permissibility of clinical research hinges upon whether or not the rights of experimental subjects are respected. Respect for rights means allowing an individual to exercise his freedom without unnecessary oversight or interference. Respect entails that the experimental subject will not be deceived, coerced, used without his consent, or against his will.

Governments, regulatory agencies, and ethicists need not protect research subjects from themselves; rather they ought to focus upon respecting the rights of experimental subjects. Each experimental subject has certain basic prima facie rights. This leads into a further defense of the ethical permissibility of clinical research: the right of self determination. The rights of the individuals ought to be respected. One of the most basic rights is the right to determine what will be done with your body and person. A competent individual ought to be at liberty to participate in a myriad of activities from bungee jumping to participating in clinical trials. The right of individuals to engage in their choice of ends is a basic prima facie right which should be respected.

Most of the concerns regarding clinical research and RCTs will be answered while analyzing a number of interrelated issues. These issues discussed in this chapter include autonomy, informed consent (in the face of uncertain outcomes), coercion, and the exploitation of vulnerable populations. Several other ethical

issues will be addressed in subsequent chapters; those issues include the supposed therapeutic obligation of the physician, the obligations of the clinical researcher, the notion of equipoise, moral codes and oaths, the FDA requirements, and the phases of drug studies.

In this chapter I argue that patients/ experimental subjects who are competent and have the capacity to exercise their individual autonomy are able to consent and ethically participate in most in clinical trials. As I mentioned in the introduction to chapter 1, I will argue that the ethical permissibility of clinical trials can be judged very simply by answering “yes” to the following questions:

- 1) Is the potential experimental subject competent to exercise his autonomy and his right of self determination in order to enroll in the clinical trial?
- 2) Is the potential experimental subject informed about the nature of risk and benefit involved in his participation in the clinical trial?
- 3) Is the trial scientifically/ epistemically valid?
- 4) Will the trial attempt to answer a scientific question or questions of value?

A trial that does not meet these four conditions is *prima facie* unethical. It may be possible to run an ethically permissible trial without meeting these four conditions, but those exceptions are few and far between. I will focus primarily upon the first two conditions, but it will be assumed throughout the dissertation that the trials being considered are methodologically sound and that the hypotheses being tested are non- trivial. Competent persons have the right to enroll in scientifically valid clinical trials so long as they are informed and consent to participate. My minimalist defense of clinical trials differs from most



defenses of clinical trials found in the literature. The right of self determination is broad enough to allow competent individuals to ethically participate in most methodologies of clinical experimentation (including both randomized trials and placebo control trials).

Competent persons have the right to decide what is done with their body and person. They have autonomy over their own person. Competent persons are at liberty to consent to participate in clinical research. This basic freedom entails the ability to legitimately consent to participate in a myriad of clinical research methodologies including RCTs and PCTs. The arguments in this chapter will form the basis for the subsequent ethical analysis of clinical research. In subsequent chapters I will address other ethical concerns and objections to specific research methodologies, including randomization and placebo control.

### **Ethical Thesis**

There has been a great debate involving philosophers, physicians, and medical researchers about the ethical permissibility of running Randomized Control Trials. There has also been a great deal of debate about the use of placebo trials. The use of both randomized trials (RCTs) and placebo control trials (PCTs) have engendered a discussion involving the World Health Organization, the FDA, clinical researchers, and philosophers. Organizations, such as the FDA, have adopted a view known as placebo orthodoxy. It is argued, by those who speak for the agency, (e.g. Robert Temple and others) that placebo trials are the optimal trial design and that they are normally ethically permissible. On the other side are those (e.g. Rothman and Michaels, 1994; 2003) who argue that RCTs serve no

useful epistemic or scientific purpose not served by other less objectionable designs. I have addressed these arguments in the previous chapter. Others (including Rothman and Michels in their influential paper) object to RCTs on ethical grounds even if they serve a needed epistemic purpose or at least provide the best form of evidence. When considering the ethical permissibility of clinical research, both philosophers and non-philosophers have tended to use either of two strategies: the first is to appeal to some general moral theory, usually Kantianism or Utilitarianism; the second is to appeal to medical codes of ethics that have been developed by professional ethicists. I reject both approaches.

In opposition to all of these critics of RCTs, my thesis is that both RCTs and PCTs, in particular, are ethically permissible. I have adopted a minimalist approach. My approach is minimalist in that it resolves most of the key issues in terms of autonomy and informed consent and does not presuppose Kantianism, Utilitarianism, or any other general moral theory. Beyond informed consent and autonomy I have added two other criteria; specifically that the experiments employ a scientifically valid methodology (design) and endeavor to test (or investigate) a hypothesis having scientific value.

I defend the ethical permissibility of both RCTs and PCTs on the basis of the patient's/ experimental subject's capacity to make an autonomous decisions. This ability ought to be respected; the basis for the respect accorded our individual autonomy is the prima facie right of self determination. This right will be explained and defended below, but, in brief, the right of self determination entails the freedom of each individual to decide for himself his choice of ends. If I am

correct that competent individuals have capacity to exercise their individual autonomy and a right of self determination then it follows that they have the ability to give their informed consent to participate in most, if not all, types of clinical trials. Individual autonomy, the right to self determination, and informed consent can resolve most of the ethical objections that are raised to clinical research. In this chapter, I challenge the appeal to Kantianism as a basis for criticizing all RCTs. In subsequent chapters, I discuss the remaining anti-RCT arguments. On the other side of the debate are those who believe that RCTs are ethically acceptable; some just take this as obvious. Others offer a defense; often the defense is based on Utilitarianism. I try to show that the appeal to a very abstract moral theory such as Kant's or Mill's is inadequate to resolve the ethical permissibility of clinical trials. My view is not entirely without a theoretical component. It presupposes that people have certain prima facie rights, and it assumes that rights are more basic (and important) than goods. Yet, having said this, my view does not require the truth of any specific moral theory.

### **Deontological Principles and Analysis**

Kantian views are often employed to criticize RCTs. The categorical imperative is Kant's supreme moral principle. He states several formulations of the categorical imperative; I will consider what are traditionally known as the first two formulations. The first formulation of the categorical imperative, also known as the formulation of a universal law of nature, is stated thusly, "*Act only on that maxim whereby thou canst at the same time will that it should become a universal law.*"<sup>63</sup> The idea is that our actions should be universalizable by others in our

same circumstance. Rationality, according to Kant, is not aimed at the individual good or self interest. For Kant, one is rational and autonomous if and only if one is acting in accordance with universal rules of behavior which are compatible with the categorical imperative. If an individual is only acting from what he believes is his prudential self interest, and in a way that is not compatible with the categorical imperative, then he is neither rational nor free on Kant's view.

There are three central issues raised by employing the first version of the categorical imperative to evaluate the ethical permissibility of RCTs:

- 1) There is a question of proof. Is the categorical imperative a valid moral principle? This is important because utilitarians (and others) will simply challenge the truth of the principle;
- 2) Often it is not clear how to apply the principle to the case of clinical trials. How can I tell whether I can rationally will that the maxim of my contemplated act of running such and such experiment be made into a universal law; and
- 3) Two reasonable people can employ two different maxims for the same act.

Firstly, the truth of the categorical imperative is not above dispute. There is not universal agreement among philosophers that the categorical imperative is a correct moral principle. Generally, philosophers don't agree on much, but there is not even a plurality of philosophers who hold the categorical imperative to be a correct moral principle. To simply assume that it is binding in this instance begs the question against rival moral theories, such as Utilitarianism. Utilitarians and others will simply challenge the truth of the principle.

Secondly, it is not clear how to apply the categorical imperative in most cases. Kant provides notoriously few examples of the application of the principle. Besides what he takes to paradigm cases such as lying or suicide, he says very little. Even so, what he does say, particularly regarding the ethical permissibility of suicide, calls into question reliance upon the categorical imperative in the practice of medicine and clinical research. I am not alone in recognizing this problem. Several philosophers have discussed this point. In Eric Matthews' paper entitled, "Autonomy and the Psychiatric Patient", he points out that employing Kantian principles can lead to a conflict between physicians and patients. Matthews considers the example of a terminally ill patient who wants to end his life. Kant himself argued that the act of suicide was not universalizable, nor was it compatible with an application of the categorical imperative. Instead of allowing for self determination or for acting in accordance with a patient's wishes Kant's moral philosophy, specifically the categorical imperative, could be applied to defend paternalism. In a case where a patient might choose a quick death over measures to prolong his life, a physician might employ a Kantian argument to defend his decision to go against the wishes of the patient.

In the case of suicide Kant would maintain that a patient who has a desire to end his life is irrational. Yet it is irrational only if you make several additional assumptions. It is irrational if one) the maxim of the action actually violates the categorical imperative and two) all actions that violate the categorical imperative are irrational. Whether this is the case or not is debatable. It is certainly possible

to imagine particular circumstances where an individual would really be better off dead.

For example, if a patient is terminally ill and suffering from great, uncontrollable pain, then the ending of his life might seem reasonable. Dying would bring an end to the patient's suffering. Could such an act be universalizable? For Kant, the answer was no, but others have applied the categorical imperative in such a way that it could be. How the categorical imperative is to be applied highly contentious. Even if one were to grant that Kant's deontology were correct, in principle, how it is to be applied in specific cases is unclear.

As for the third point: From the perspective of a clinical researcher, different researchers could employ different maxims as they consider the ethical permissibility of conducting a clinical trial. By the same token, different patients may also employ different maxims when considering enrolling in clinical trials as well. At times, depending upon the maxim willed, it can rationally be willed to be a universal law and at other times it cannot. A key problem for Kantians is that for the very same act, say including a placebo control, there can be many different maxims, some of which are universalizable and some of which are not. If this is true, then it will be both morally permissible and morally impermissible, depending on the maxim of one's act, to include placebo controls or to randomize.

Application of the categorical imperative, as discussed above, is more complicated than most contemporary writers admit. The second version of the categorical imperative is often discussed when considering the rights of patients.

Kant calls this a “supreme practical law”, the principle of humanity: *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 means only.*<sup>64</sup> Some of the “Kantian” defenses of patient rights are based upon the statement above. How one is to interpret the notion that a person should never be employed as a “mean only” can lead to considerable disagreement.

Is it compatible with the categorical imperative to will that one should be a participant in a Randomized Control Trial? Is the doctor simply using me as a means to an end, thereby violating my inalienable humanity? These questions can be answered in a myriad of ways; this is because there are several competing (and legitimate) interpretations of how to apply Kantian principles.

Contemporary writers, such as Beauchamp and Childress, employ the principle of humanity to argue that “respect for autonomy flows from the recognition that all persons have unconditional worth”<sup>65</sup>. They discuss the principle as though it obviously true, and as though it could stand alone- absent of any theoretical foundation. Removing a single moral principle from the context in which Kant employed it robs it of its axiological force. By removing the principle from the context in which Kant presented it you also remove it from the arguments he employed in its defense. These arguments could be employed, but it would involve an understanding and reconstruction of Kant’s philosophy. This seems to be beyond the scope of most of the biomedical discussion regarding patient’s rights and the ethical permissibility of clinical trials.

### **Kant on Autonomy**

Kant's views on autonomy are also often taken out of context in order to support patient rights. In his writings Kant uses both the term 'autonomy' in at least two senses. At times Kant uses the term autonomy in a metaphysical sense, at other times he uses it in a moral sense. Kant believes that we must be free in a metaphysical sense in order to be held accountable for our actions. Some philosophers have taken the position that we are not free, other have maintained that we are. Ultimately, in my view, the question of our metaphysical freedom remains unresolved. I hold that people can have the capacity to act autonomously even if we lack metaphysical autonomy. My position does not presuppose metaphysical freedom (freedom of the will) in order for persons to have the capacity to act autonomously.

The following passage, taken from The Foundation of the Metaphysics of Morals, recapitulates his view on autonomy:

*The Concept of Freedom is the Key to the explanation of the Autonomy of the Will. WILL is a kind of causality belonging to living beings in so far as they are rational, and freedom would be that property of such causality that it can be efficient, independently of alien causes determining it; just as natural necessity is the property that the causality of all nonrational (irrational) beings to be determined to activity by the influence of alien causes.<sup>66</sup>*

For Kant, as supported by the passage above, rational wills are free, whereas irrational wills are not. A necessary condition of one acting autonomously is that one be rational. On his view, we must postulate ourselves as being "free", in a metaphysical sense, if we are to consider ourselves as moral agents. In support of this interpretation, I cite the following passage, "the idea of freedom the concept



of autonomy is now inseparably combined, and with the concept of autonomy the universal principle of morality, which in idea is the ground of all actions of rational beings, just as the law of nature is the ground of all appearances.”<sup>67</sup> He says that all of our actions, ideally, would be performed in accordance with the “universal principle of morality” (the categorical imperative). If an individual is acting in accordance with the categorical imperative then he is autonomous, when he is not acting in accordance with the categorical imperative, he is not autonomous.

Moral autonomy is exercised when our actions are arrived at by means of reason and the maxim of the action is compatible with the categorical imperative. The idea is that our actions, in order to be considered rational, must be universalizable in accordance with the categorical imperative. It should be noted that rationality is not aimed at the individual good or our self interest. What is important to note is that the conception of autonomy being presented here is radically different from the type of autonomy that is often discussed in contemporary bioethical debates. In part this is because Kant ties a unique interpretation of rationality to the concept of autonomy. His notion of rationality and autonomy are distinct from how the terms are employed in the contemporary discussion regarding clinical research.

The interpretation of Kant’s philosophy is no easy matter. Numerous papers have been written on this issue. One such paper by Barbara Seeker discusses how Kant’s deontology has been misunderstood in the bioethical literature. She illustrates this by citing one of the “less sketchy” interpretations of Kant’s notion

of autonomy which can be found in a popular bioethics textbook by Mappes and DeGrazia titled Biomedical Ethics. Mappes and DeGrazia summarize the Kant's principle of humanity and notion of autonomy as follows:

What Kant calls 'dignity of man as a rational creature' is due to human beings having the property that enables them to govern their own actions in *accordance with rules of their own choosing*. Putting aside many complexities in Kant's own thinking, a Kantian position central in biomedical ethics describes autonomy in terms of self-control, self-direction, or self-governance. The individual capable of acting on the basis of effective deliberation, guided by reason, and neither driven by emotions or compulsions nor manipulated or coerced by other is, on the Kantian position, the module of autonomy.<sup>68</sup> (My emphasis)

This particular "Kantian" view of autonomy does not seem compatible with Kant's principle of autonomy. First of all, the categorical imperative is not an arbitrary rule. It is a universal rule of morality. It is a rule that governs the behavior of all rational beings. It is a rule that all rational beings are universally bound by. The idea that rational beings are autonomous when they act "accordance with rules of their own choosing..." makes it seem as if moral rules are arbitrary or subjective. Imperatives of practical reason are not subjective in the way suggested above. This is not what Kant has in mind at all. It is not a principle that is relative to the individual's interest or desires; it is an absolute rule

of morality. It is a rule that is binding upon all rational beings. As Kant's views are interpreted by Mappes and DeGrazia his deontology collapses into relativism.

Most contemporary writers assume that when Kant talks about autonomy, that he means one's capacity or right to make decisions. An example of such an autonomous decision might be to end one's life, yet, for Kant, this is not the case. Eric Matthews draws the following conclusion from his analysis of the term "autonomy" as found in Kant and in the modern bioethical literature: it follows that Kant's conception of autonomy differs in significant respects from that employed by modern medical ethicist, and so that Kant's argument for respecting human worth cannot be used to justify the modern principle of 'respect for patient autonomy'.<sup>69</sup>

When Kantian ethics is employed as a defense of patient rights, without further analysis or argument, the defense fails. Autonomy, as employed by Kant, bears little resemblance to the notion as it is discussed in the contemporary literature. Boggled down by Kant's metaphysics and deontology, it is not a good foundation for a defense of a patient's rights or for evaluating the ethical permissibility of clinical trials.

### **Utilitarian Defenses of Clinical Trials**

Utilitarian arguments are often employed to support or defend the ethical permissibility of clinical trials. The central problem with a Utilitarian justification for the ethical permissibility of clinical research is that trials which systematically violate the rights of experimental subjects could routinely be judged acceptable. This results from the fact that the theory says nothing about the distribution of the

good effects, say happiness. The number of people who will benefit from unethical experiments will often be much greater than the small number of people participating in the experiments. Further Utilitarianism licenses too many unethical experiments, even Nazis experiments where people are forced to participate, but also milder ones where there is possibly any of the following: deception, coercion, exploitation, no informed consent, experiments using children, the elderly, prisoners or other vulnerable populations as subjects.

Utilitarians try to block the objection by appealing to the long run, but what is the long run? Is it 10 years, 40 years, or even 100 years? Whatever time period is picked will be arbitrary. A second problem is that there is often no way of knowing whether in the distant future, the bad effects of an ethically objectionable experiment will swamp the good effects. In practice, utilitarians often decide on intuitive grounds which experiments are unacceptable and which are not, and then use the claim about long term bad effects to condemn the former. But since they provide no evidence to support the claim of long term bad effects and are deciding beforehand on intuitive grounds which experiments are bad, they are not really using Mill's principle to decide the issue.

The beneficial consequences of developing new medical interventions are often weighed against the cost to the experimental subjects who participate in the clinical trials. There have been numerous cases, particularly with HIV trials conducted in Africa, where Utilitarian calculations seem to have been employed to justify clinical trials. In one instance placebo control clinical trials were conducted on pregnant women with HIV to determine the rate of transmission

between the mother and child. Prima facie, given the risk to both the mother and unborn child, these trials appear to be unethical. From a utilitarian perspective, one might argue that the cost of a few hundred test subjects would be a small price in order to develop a cure for HIV/AIDS.

A clinical researcher might argue for the use of a placebo control group by maintaining that these people were going to die anyway. If there were no trial, then they would have had no hope of survival. Simply because there is a trial it does not follow that all of the participants are entitled to receive the medical intervention. In the end, at least some of the trial participants will receive an experimental medical treatment. Most commentators would find research conducted in this manner unethical.

Trials of this type are not only conducted in developing countries; early clinical trials for polio conducted in the United States were justified in part on the basis that the reward of finding a cure for such a debilitating disease was worth the risk of crippling a few hundred (or thousand) children in the process of testing an unproven vaccine. In the end, many children were crippled, in a rush to find a cure. A utilitarian could maintain that the cost to those children was outweighed by the benefit to all of humanity. The Nazis also employed utilitarian justifications for some of their experiments conducted on unwilling prisoners during WWII. The Nazi experiments will be considered in more detail in chapter 4. When there is a great need, especially in cases where there is an epidemic, Utilitarian justifications are often employed to justify infringing upon or violating the rights of test subjects. Such experiments may be ethically permissible from a

Utilitarian perspective, but they would violate my minimal standards for ethical research.

### **Mill's Defense of Individualism and Autonomy**

Another defense for both the right of patients and for RCTs can be based upon John Stuart Mill's philosophy. In his essay "On Liberty" Mill is defending individualism against the paternalism of the state. I feel that this defense can be extended into other areas, including clinical research. Opponents of this view, (e.g. Benjamin Freedman) argue that this appeal to the liberty of research subject to enroll in clinical trials fails. Freedman's arguments will be considered in detail in the next chapter. I argue that such a defense of clinical trials can succeed. Why is it that most people feel that persons have the right to decide upon their own choice of ends in other areas of life, but when it comes to clinical research the rules change? What morally relevant difference is there between allowing people race cars at the track and letting them engage in a clinical trial. It seems obvious that enrolling in a clinical trial is a more laudable endeavor than drag racing your car, yet some paternalistic ethicist is going to try to restrict your liberty in this instance.

Returning to Mill, he argues in his essay "On Liberty" that "the only freedom which deserves the name, is that of pursuing our own good in our own way, so long as we do not attempt to deprive others of theirs, or impede their efforts to obtain it. *Each is the proper guardian of his own health, whether bodily, or mental and spiritual.*"<sup>70</sup> (My emphasis). In his essay Mill argues that individualism, which we can take as the right to exercise our individual

autonomy, is of paramount importance to humanity. It is an essential right. I defend our right to enroll in clinical trials on the basis that each competent person has a prima facie right of self determination. The discussion of this right, and its similarity to Mill's individualism, will be considered below.

As in the case of Kant, Mill is not without his philosophical jargon. Although, in my opinion, not as great a burden as Kant's system, Mill's individualism ought to be put into the context of his Utilitarianism. It is unclear to some philosophers as to whether the two ideas can be reconciled, although I argue that they can. Mill's moral theory is based upon Jeremy Bentham's principle of utility. Mill accepts and builds upon Bentham's ethical theory. Utilitarians argued that the right action is the one that will augment happiness the most or, where that is not possible, diminish happiness the least.

The conflict that results between individualism and the principle of utility is as follows: the individual interest is often in conflict with the aggregate of utilities. Our individual interest is often in conflict with the common good or the interest of society. For example, one may desire to be a painter, but society may be better served if he enlisted as a soldier. In this instance, if utility would be maximized by forcing the individual into a job he does not desire, then the common good would seem to trump individual freedom. In the case of clinical research, forcing a few individuals, against their will, to participate in medical experiments might serve the needs of the entire society.

As a note of clarification, most utilitarians, including Mill, would not support such a position. Yet, why is this the case? As noted earlier, it seems that when an

act looks horrendous from a moral point of view, and yet seems to increase overall utility, the Utilitarian will say that in the long run more harm than good will be done. But since he can always say this with or without evidence, how does use of the Principle of Utility answer the questions about the ethics of placebo controls or the use of any sort of RCT? It looks as if the Utilitarian determines first if there is a net gain in utility in the short run and then decides on intuitive grounds if the act is immoral. If it is seemingly immoral, then the utilitarian says: sorry, there will be a loss of utility in the long run. If it looks okay from a moral point of view, then they do not say this. But, then, is the Principle of Utility really being used to decide things? The answer seems to be no.

Mill claims that individual freedom is of greater importance than the common good. His essay "On Liberty" is primarily an argument aimed at paternalism by the state and a defense of our individualism. Mill argues against the interference of the government into the private affairs of competent individuals. The essay can also be seen as an attempt at a reconciliation of utilitarian and liberalism. Mill's essay "On Liberty" can be seen as a response to the tension between these competing goals. A resolution to the apparent incompatibility of these two doctrines can be stated as follows: The cost of sacrificing our individuality (the right to exercise of our individual autonomy) outweighs the benefit of forcing an individual to perform an action or function that violates his individual autonomy. In Mill's view such interference is unjustified regardless of whether the society is acting for the common good or the individual's own good.



Applying this conception of autonomy to clinical research, and agreeing in principle with Mill, Hans Jonas points out “it may well be the case that the individual’s interest in his own inviolability is itself a public interest such that its publicly condoned violation, irrespective of numbers, violates the interest of all. In that case, its protection in each instance would be a paramount interest, and comparison of numbers will not avail.”<sup>71</sup>

When considering the ethical justification for clinical research, one of the central arguments is the potential benefit to mankind. The idea is that the consequences of clinical research, the benefits reaped by mankind, or the common good, can outweigh the harm caused to the individual. On the surface the rights of the individual seem to be at odds with this notion. Instead of enrolling a patient in a study that involves a risk of receiving a placebo or ineffective treatment, the patient’s interest would be best served by giving them standard therapy.

In many cases it is true that the research will have no benefit to the patient, or might result in harm to the patient’s long term health. In those cases, the patients should be informed of the potential risk or potential benefit and then be allowed to decide for themselves if they want to participate in the research. Each individual has the right to choose to participate in a clinical study. Once the individual has been provided the required information regarding risk and benefit involved with the research, he should be left alone (not allowed, for no one needs to give him permission) to make a decision. I would argue against any paternalistic interference in the decision making process by the physician. Further I would

argue just as vehemently against a utilitarian who proposed violating the patient's autonomy of the basis that it would benefit the common good.

Again the main focus of Mill's essay is an argument against paternalism. Mill's central thesis, also known as the Harm Principle, can be stated as follows, "the sole end for which mankind are warranted, individually or collectively, in interfering with the liberty of action of any of their number, is self-protection."<sup>72</sup> In his view, society should not intervene in the affairs of one of their number for any other reason than self protection. This notion can be extended beyond political associations and into other areas, such clinical research. Physicians and researchers should not interfere in the decisions of competent persons who choose to enroll in clinical trials. This assumes, of course, that the individual in question is rational and in control of his faculties.

An autonomous individual, in Mill's view, is one that has full maturity of his faculties. He points out that, "We are not speaking about children, or of young persons below the age which the law may fix as that of manhood or womanhood. Those who are still in a state to require being taken care of by others must be protected against their own actions as well as against external injury."<sup>73</sup> In fact, in those cases special precautions must be taken to ensure that the rights of the individuals are not violated. This idea of competency will have bearing on the discussion of vulnerable patient populations, to be considered later.

### **Respect for Individual Autonomy and the Right of Self Determination**

Individual autonomy is the capacity to be one's own person, to live one's life according to reasons and motives that are taken as one's own and not the product

of manipulative or distorting external forces. Individuals with this capacity are able to freely consent to participate in clinical research. Prima Facie, an individual's capacity for autonomous decision ought to be respected. Competent persons have a right of "self determination" as Alan Goldman terms it. He defines this right as the right to have "control over decisions vital to the course of one's life." <sup>74</sup>

Although I am not interested in explicating the necessary requirements for moral accountability, I would argue that if an agent has the capacity to exercise his individual autonomy, and is free in the sense that he is acting in accordance with his own beliefs and desires, then he may be held accountable for those actions. If we are the author of our actions, then that is sufficient to hold us accountable for them. There are several other criteria that must be met in order for an agent to be autonomous.

The capacity for autonomous action can be affected by several internal and external factors. Externally, one must be free from external interference. For example, if I push you down every time you attempt to open the door, then I am affecting your ability to perform an autonomous action. I may also threaten you with harm. If my threat forces you to alter your behavior then I have placed an external impediment to your ability to make an autonomous decision.

On the other hand, one must have at least one internal capacity: rationality. If I cannot make a rational decision, then it would seem that I cannot act autonomously. Young children lack a developed capacity for rationality, as such they are normally not considered autonomous. Other people may suffer from

psychological disorders which hinder their ability to perform rational calculation, arrive at rational decisions or perform autonomous actions. Specifically some individuals suffer from compulsions or unwanted desires that affect their decisions. Persons that lack rationality generally do not have the capacity to exercise their individual autonomy, their personal liberty, or their right of self determination. Individuals that are irrational or not competent do not necessarily have a right of self determination.

Ultimately, I feel that Mill's views are much more relevant to the current discussion, and can serve as a legitimate, defensible foundation for a doctrine the right to self determination and respect for our individual autonomy. From the concept of a prima facie right to self determination and respect for the individual autonomy, we can derive and support particular rights of individuals as well as corresponding obligations others have to them. Autonomy is at once a capacity, the ability to make a rationally decision about means and ends, and it is a right. It is the inherent right of individuals to make choices about their interest, values, and ends. As a point of clarification, when I speak of "respect for individual autonomy" I mean that to say that a person's autonomy ought to be respected and that he has the capacity to act autonomously and that he has a right to act without interference.

The foundation for this right to exercise our individual autonomy is the notion of a right to self determination. The right of self determination is prima facie in nature. As a prima facie right, in principle, it could be overridden by another right in certain circumstances, but, in general, it should not be overridden. It is such a

basic and important prima facie right that it should seldom, if ever, be overridden by any other right or obligation. This is the case because there will seldom, if ever, be situations where another prima facie right or obligation is more important than our right of self determination.

I would like to differentiate the type of autonomy to which I refer from others that may be found elsewhere. The type of autonomy to which I refer is individual autonomy. The version of autonomy which I defend is most closely associated with the views of Mill. Autonomy consists in one being able (having the capacity) to act in accordance with his own beliefs and desires (to make choices) without external interference. Respect for individual autonomy requires that one not interfere with the choices and decisions of other individuals. This assumes that those choices do not interfere or harm the rights of others. No one should impose his will upon another without justification. Jim's autonomous decision to perform an action should be respected by Sam so long as the action does not bring about harm to another.

Each individual has a prima facie right of self determination; this right is akin to a basic right of liberty. It is the freedom or liberty to engage in ends of our own choosing without unjustified interference from others. We need not justify our choice of ends to others as long as those choices do not infringe upon their rights. Respecting our right of self determination and our capacity to act autonomously is essential for ethically permissible clinical research. The basis for this conception of autonomy is personhood. Personhood entails the freedom or liberty to act without being constrained by another's choice, insofar as it can coexist with the

freedom of every other. The right of self determination, broadly construed as the individual's basic liberty to make choice that effect his future and his person, may be a prima facie right, but it is one that carries a great deal of weight and should seldom, if ever, be overridden by other competing prima facie rights or obligations.

The right to exercise freedom over our person and to have freedom to choose our ends and goals is a right that is essential to our very being. When philosophers such as Thomas Hobbes or John Locke discussed a natural right to liberty, this, in part, is what they have in mind. I will not, go so far as to claim that this right of self determination is a natural right (although I believe that such a defense could be given).<sup>i</sup> At this juncture I claim that it is a prima facie right, one that is generally at or near the top of any hierarchical ranking of prima facie rights.

Given the importance of this right, clinical researchers should not violate it. This right should not be infringed upon by either force or fraud. Clinical researchers should not coerce individuals into participating in clinical research, nor should they deceive them by either withholding information about the risk or by over stating benefits. In general, the right of self determination allows autonomous individuals the freedom to evaluate and determine their choice of ends and goals. One is free to ride bulls, wear a pink neck tie with a green shirt (as per Goldman), bungee jump or even participate as an experimental subject in a Randomized Control Trial with a placebo control! A research subject has the

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<sup>i</sup> For a more extensive discussion of natural rights please Lemos, Ramon. Rights, Goods and Democracy. Newark: University of Delaware Press: 1986: 45-63.

right to enroll in research, but researchers also have an obligation to respect his right to refuse participation in research.

Respect for our autonomy entails that one is at liberty to act in accordance with his choices without external interference. If one is forced by another to perform an action, then his autonomy is not being respected. Further, if you make decisions for other people then you are not respecting their autonomy, their right to choose. The right of self determination is a *prima facie* right of great importance.

In the context of medical research, the rights that follow from being an autonomous individual, *ceteris paribus*, are more important than the knowledge that may be gained for the betterment of society. The individual's rights take precedent over the supposed interest of the common good. As Goldman says, "Rights express interest of individuals important enough to be protected against additions of lesser interest across persons. When they are exercised, the resultant claims to goods or freedoms are to be honored even at the expense of the aggregate collective welfare. The number of people with opposing lesser interest becomes irrelevant when a right is at stake."<sup>75</sup> In other words, the addition or increase of individual utilities, no matter how great, is ethically impermissible if the gain is the result of sacrificing or violating the rights of persons. This principle should hold even if it is just the rights of one person in question, and the masses would benefit greatly from violating the rights of this person. In Goldman's view, (and I agree), rights are more basic than goods.

In the past, the rights of the individual has been systematically ignored and violated on the grounds that it served the overall utility gained: the common good. In other words, utilitarian calculations should not be employed in an effort to systematically violate the rights of persons. It would seem that any justifiable research involving human subjects ought to serve an epistemic need (in other words, the research should be both non-trivial and serve to further human knowledge). At the same time it must be morally justifiable. The Tri-Council of Canada suggests the following as possible legitimate goals for research:

Research involving human subjects is premised on a fundamental moral commitment to advancing human welfare, knowledge and understanding, and examining cultural dynamics. An ethic of research involving human subjects should include two essential components: (1) the selection and achievement of morally acceptable ends and (2) the moral acceptable means to those ends. The first component is directed at defining acceptable ends in terms of the benefit of research for subjects, for associated groups, and for the advancement of knowledge. The second component is directed at ethically appropriate means of conducting research.<sup>76</sup>

In other words the goals of research ought to be important enough to allow for the possibility of harm to a human being. The means employed in the research, however, should be morally acceptable thus avoiding the often used argument that the “ends justify the means”. At the very least this requires that the rights and autonomy of the individual not be violated. Although this seems apparent there are a plethora of moral theories, many of which when put to the test, appear to disagree with this assessment. Respect for the individual autonomy is but one of many moral concepts that can be employed to judge the ethical permissibility of clinical research. Ultimately judgments of ethical permissibility may vary depending upon the ethical theory employed.



I maintain that a patient's right of self determination can justify, from an ethical perspective, most clinical research. The right of self determination entails the right of a patient to exercise his freedom to voluntarily choose to participate in most clinical research. The patient, as an autonomous being, in full control of his faculties, ought to be at liberty to decide to consent to participate in a clinical research study.

Self determination is a basic right of each person. The capacity to exercise our individual autonomy has value and ought to be respected within the context of clinical research and beyond. An autonomous individual has the right to consent to participate in clinical research. In order for the experimental subject to reach an informed decision the clinical researcher must provide them with the requisite information regarding the risk and benefit involved in their participation in the clinical trial. A necessary requirement of a potential experimental subject making an informed decision is that the clinical researcher provides them with the necessary information to facilitate this decision. As such, the clinical researcher has a duty to provide the potential test subject with the requisite information regarding the potential risk and benefits of their participation and to obtain their informed consent.

Although a patient has a right to enroll in a clinical trial, he cannot act completely autonomously if he is misinformed or deceived into participating in the trial. A patient cannot exercise his right to self determination in a manner that protects his interest, if he is deceived or misinformed about the risk or benefit involved in the clinical research. The physician has a duty to provide the patient

with information concerning the known risks and benefits involved by his participation in the research thus allowing the patient to become “informed”. The patient, once given the requisite information, may then engage in rational deliberation, weigh possible alternatives. After the patient has done this he may decide to consent or decline to participate in a clinical research study.

### **Informed Consent**

When individuals give their consent, they are giving permission to another to do something over which they have authority. In the context of clinical research if persons give consent they are giving the clinical researcher permission to perform the particular examinations or procedures involved in the study upon their person. They are giving the researcher permission to use their body in order to conduct experiments. In some cases they may directly benefit from these experiments, yet, in most cases, they will not. In the last century consent requirements were strengthened, in part, because of the atrocities that had befallen research subjects. It has been argued that given the risk involved in clinical research, a stronger version of consent is required: informed consent.

In order to give “informed consent” a potential experimental subject must be informed of all the relevant information pertaining to his participation in clinical research. This assumes that the person is competent to give his informed consent. It also assumes that he understands, in general terms, the nature and the risk involved of the clinical research that he is consenting to participate in. If he is not competent or do not understand the risk involved, then this condition has not been met and the research is prima facie unethical.

Informed consent is the process by which “fully informed” patients can participate in choices about their health care. What “fully informed” entails might seem unclear to some, but it need not be so complicated. Some argue that patients are informed so long as no information is willfully or purposefully withheld that would have swayed their decision. For example, if the researchers fail to disclose that in previous experimental trials the mortality rate of experimental subjects was 25%, then that omission would preclude experimental subjects from giving their “informed consent”. All known information about side effects ought or benefits ought to be disclosed to patients before they are asked to enroll in clinical trials.

According to the American Medical Association, “Informed consent is more than simply getting a patient to sign a written consent form. It is a process of communication between a patient and physician that results in the patient's authorization or agreement to undergo a specific medical intervention.”<sup>77</sup> The notion of informed consent as a process is problematic in that the procedures for engaging in this process are not uniform across the spectrum of research settings. In some settings research subjects interact with their personal physician. In other settings they deal with a clinical researcher or a technician that reviews the informed consent document with them. In most cases of clinical research, a research participant will sign an “informed consent” document.

According to current legal and moral standards, the informed consent document should detail: The patient's diagnosis, if known; the nature and purpose of a proposed treatment or procedure; the risks and benefits of a proposed treatment or procedure; alternatives (regardless of their cost or the extent to which

the treatment options are covered by health insurance); the risks and benefits of the alternative treatment or procedure; and the risks and benefits of not receiving or undergoing a treatment or procedure.<sup>78</sup>

The ability to give informed consent varies depending on the type of research being conducted, as well as the type of experimental subjects participating in a research study. Certain populations, such as children, cannot give informed consent. In such cases, any proposed research must be closely scrutinized. I argue that informed consent is a necessary requirement in almost all cases for research to be ethically permissible. In cases where it can be obtained, then it must be obtained. If consent is not received from a competent experimental subject, then the research is unethical. I argue that informed consent can answer many of the ethical concerns and objections raised to clinical research.

Tied to the notion of informed consent is the fact that researchers must give full disclosure of all known the risk and benefit associated with the clinical trial. If researchers deliberately withhold or omit information pertaining to risk, then I argue that the research is unethical. Consent that is obtained by fraud or deception is not “informed” and is not a legitimate ethical foundation with which to conduct clinical research. It has been argued that “patient consent, given after receiving a certain (and tangentially increasing) amount of information, is not one, *but the only source of the legitimization of the care provided by a physician to all conscious and competent patients.*”<sup>79</sup> I claim that consent is essential in both patient care and clinical research.

There are a number of concerns that can be raised with this concept. One concern involves what being “informed” actually entails. It has been argued that “fully informed consent” is unobtainable in practice. Hans Jonas argued that only a physician-researcher is qualified to provide “fully informed consent”. In Jonas’s view this is because only the physician/ scientist is in a position to completely understand the risk and benefit entailed by participating in a research study. He claimed that to explain the research in lay terms was not sufficient for a potential subject to give his “informed consent”.

Hans Jonas argued for a strong (or extreme) knowledge requirement as a necessary condition of obtaining informed consent. This requirement would only be met in a few cases. Most clinical research conducted in the last fifty years would fail to meet this requirement. Only the Bruce Banners of the world, working in their laboratory with deadly (and unpredictable) gamma radiation can actually grasp the potentially dangerous side effects of such research. (In Dr. Banner’s case, he still ended up turning himself into the Hulk. The rest of us, given our ignorance of clinical research and medicine, would have never seen that as the remotest possibility.)

Jonas argued that employing a physician as a research subject would be the ideal because he would be fully cognizant of the potential risk, benefits, and the biological methodology involved in the research. In his view the physician is uniquely qualified because of his scientific knowledge. This notion has been ridiculed by many commentators.

Although this position has been ridiculed and, for the most part, ignored, it still represents one interpretation of how the informed consent requirement may be satisfied. Again Jonas argues that only a select few individuals have the requisite knowledge to grasp the risk and benefit involved in clinical research. On his view, if you do not have a background in clinical research, then you cannot provide informed consent. He argues that particular aspects of the risk involved in clinical research cannot be boiled down to terms that a layperson can understand. If he is correct, that experimental subjects cannot understand the risk, then it may follow that they cannot give their informed consent. This view could be termed as a strong knowledge/ understanding requirement for informed consent. This requirement could only be met by a select group of highly trained individuals.

On another extreme, it is possible to argue that informed consent is not a necessary requirement for ethically permissible clinical research. In a controversial article titled, "Is Informed Consent Always Necessary for Randomized, Control Trials" Robert Truog and Walter Robinson point out that in the context of clinical care a physician could conduct an experiment without any oversight (from the FDA or an IRB) or the knowledge of their patients.<sup>80</sup> They do not endorse conducting research without obtaining informed consent, but they seem to think that this happens within the context of clinical care quite often.

A more moderate position is that most competent individuals are capable of giving their informed consent to participate in clinical research. I believe that most, if not all, competent individuals, if provided the necessary information in an

understandable manner, can give their informed consent. I term this a moderate knowledge/ understanding requirement. This is the current norm that has been adopted in the practice of clinical research. Consent is obtained from experimental subjects from various walks of life. Few, if any, of the subjects involved in clinical research and participating in clinical trials have formal training in clinical research or more than a basic understanding of what the research entails.

I think that most competent adults, in full possession of their faculties, can give their “informed consent”. I do not believe that you need any formal medical training, nor do you need to be a clinical researcher to provide informed consent to participate in clinical research. I believe that the risk and benefits of participating in clinical research can be explained in a manner so that any competent person can understand the danger and the reward involved. I think that many of the problems with informed consent have been overstated. Consider the argument of Benjamin Freedman below as just such an example. In this paper he argues for “ignorant consent”.

In his paper titled, “A Moral Theory of Informed Consent,” Benjamin Freedman put forth the following view of informed consent:

In truth, a reductio ad absurdum of this view of “informed consent” need not be constructed; it serves as its own reductio ad absurdum. For there is no end to “fully informing” patients. When the doctor wishes to insert a catheter, must he commend to the subject’s attention a textbook on anatomy? Although this, of course, would not suffice: he must ensure that the patient understands the textbook as well. Must he tell the patient the story of Dr. X, that bogey of first-year medical students, who, in a state of inebriation, inserted (“by mistake”) his pen-refill instead of a catheter? With, of course, the assurance that this physician never

gets drunk. (“Well, rarely, anyway.”) Must the patient be informed of the chemical formula of the catheter? It’s melting point? <sup>81</sup>

Freedman argues that “fully informed” is so far beyond the reach of the average patient or test subject that it is, in his words, “a reductio ad surdum”. I am not sure that Freedman actually understands what “a reductio ad surdum” means, but from the context (and with a charitable interpretation) it appears that he means that “fully informed consent” is an oxymoron: it is impossible to obtain in practice.

The quote above gives a great deal of extraneous information; information that is not related or required for a researcher to obtain informed consent. It is implausible to argue that when people discuss “informed consent” that they have anything like what is discussed above in mind. A test subject does not need to know of every medical error ever made in order to give his informed consent; he simply needs to be told basically the risk and benefit involved in his participation in the clinical trial.

Freedman argues that “fully informed consent” is impossible to attain; to that end he argues that, “Our main conclusion, then is that valid consent entails only the imparting of that information which the patient/test subject requires in order to make a responsible decision. *This entails, I think, the possibility of valid yet ignorant consent.*”<sup>82</sup> (*My emphasis*)

What Freedman means by “valid yet ignorant consent” is unclear. I feel that it is a poor choice of terminology. If anything it is open to just as much criticism as Freedman himself employed towards Jonas’s position. Although the precise amount of information given to the patient or test subject may be debatable, it is



clear that he must be given enough information so as to be able to make an informed judgment as to whether or not he wants to participate in the research.

Instead of using the term “fully informed consent” or “ignorant consent” it might be better to use a term such as “sufficiently informed”. In Freedman’s own words, “the patient must be informed so that he will know what he is getting into, what he may expect from the procedure, what his likely alternatives are- in short, what the procedure (and forbearance from it) will mean, so that a reasonable decision on the matter may be made.”<sup>83</sup> If an experimental subject were given information so that he could meet the conditions above, then I would argue that he is in a position to give “informed consent.”

In the quote above, Freedman may not call it informed consent, but that is exactly what I have in mind when I argue that informed consent is a necessary requirement of ethically permissible clinical research. The potential experimental subject must, to employ Freedman’s words, “know what he is getting into”. If the patient has a clear conception of the risk involved, if not the science, then he can provide informed consent.

Again, I think that there is a middle ground between these two extremes. One need not be informed in the strong, Jonasian sense, nor should one give “ignorant consent” as Freedman maintains. Nor should informed consent not be obtained as some may claim. Although it would be an ideal situation if we could employ scientists or physicians as the subject of experiments, (from the stand point that they could fully comprehend most if not all of the aspects of the experiment), it is not necessary to have such an understanding for a competent individual to

legitimately consent to participate in an experiment. This again would be a strong knowledge/ understanding requirement for informed consent.

I think that a moderate knowledge/ understanding requirement is sufficient for an individual to give his informed consent. So long as individuals are given the requisite information so that they can make an informed decision about how the research experiment may affect their well being, then they satisfy this condition. An essential (and necessary) condition (in cases involving competent individuals) for any clinical research being ethically justified is that experimental subjects provide their voluntary informed consent.

On the other hand, “ignorant consent” is exactly what needs to be avoided. It is unethical because test subjects do not understand what they are consenting to. If the standard of what counts as informed is placed too low, then the patient’s rights have been violated. If a potential research subject is so uninformed (misinformed) that one could deem them ignorant, then he is not in a position to give “informed” consent. He cannot give informed consent because he is ignorant as to what he is consenting to.

### **The Ethical Permissibility of Trials Employing Persons that cannot to give Informed Consent**

There are several cases where obtaining informed consent is impossible. In those cases where obtaining informed consent from the research subject is impossible, the studies may still be ethical permissible given certain other conditions are met. Research upon subjects that cannot consent should be regulated, limited, and restricted. I think that the ethical permissibility of trials

upon subjects that cannot consent varies depending upon several factors. The factors that have bearing upon the ethical permissibility of such trials include: the potential risk and benefit to the experimental subject; the severity of the subject's condition and the importance or value of the knowledge gained by the clinical research. The specific features that are required in order for those studies to be ethically permissible will be examined in due course. Further analysis of this requirement will be provided in subsequent chapters.

Rationality is essential for autonomy. Part of the reason for claiming that children are not autonomous beings is that they lack a full understanding of the consequences of their actions. They are not able to perform rational deliberations and determine what is in their self interest. In short, they are not fully rational. They may have the potential for rationality, but they are not rational at present. It seems that this is something that changes with time.

It is true that if patients do not have the capacity (ability to reach a rational decision) to exercise their individual autonomy, then they cannot enroll themselves in clinical research. Individual autonomy and the capacity to give informed consent seem to be essential components of ethical clinical research. A competent person must have the ability, in principle, to reach a rational decision; those beings that lack this capacity are not autonomous agents.

All competent persons should be respected and treated as autonomous agents. They should be allowed to participate in or choose to refrain from clinical research. By the same token those individuals who are not competent must be respected as well. But respect in the case of those that are not competent (and

thereby not able to exercise their individual autonomy) means they should be protected. They do not have a prima facie right of self determination in the same way as a competent adult. Those individuals who are not competent to consent to clinical research ought to be protected as much as possible from the risk inherent in clinical research. They should not participate in such research unless there is a prospect of direct benefit for their medical condition. Although they cannot consent, consent should be obtained from their parents or guardians.

In cases where the patient is not competent to consent, then every possible measure ought to be taken to ensure that their rights and interest are protected. Even parents and guardians should not have complete freedom to subject their wards to any sort of clinical research. It is one thing to make a decision regarding your own welfare; it is quite another to make it for someone else. One would hope that parents and guardians would have the best interest of their ward in mind when they made such a decision, but this is not always the case. In such cases, the interest of such individuals may best be served by oversight and an ethical review process.

In general, regardless of a person's competence, the physician should not presume to have the authority or right to enroll a patient in clinical research. Likewise the physician should not presume to have the authority to exclude a patient (without justification) from research either. This is consistent with my earlier criticism of paternalism, because in a circumstance where an individual is not competent to consent to research a measure of paternalism is necessary and

required. Although I have argued against paternalism in cases where one is fully competent, I think it is necessary in cases where an individual is not.

### **Coercion, Compelling Interest, “Undue Influence” and Exploitation**

Informed consent can answer many of the ethical concerns raised to the ethical permissibility of clinical trials, but it does not resolve all concerns. Some argue that clinical trials where informed consent has been obtained from the experimental subject are still ethically objectionable. It is still possible for people who have given consent to be coerced or exploited into participating in clinical trials. These concerns will be addressed below.

Under the current structure of research that has been adopted and endorsed by the FDA, most patients in clinical trials understand that they are receiving no direct benefit from their participation in a study. The majority of test subjects consent to experimentation because they are compensated financially. They spend their time in a clinical setting, receive treatments which may be of no direct benefit to them, and risk deadly side effects. In most cases they do this for money. If you are willing to sign an informed consent agreement that states, “Any drug can, very rarely, cause allergic reactions that can be fatal”<sup>84</sup>, then I argue that this is your right based upon a conception of individual autonomy and the right of self determination argued for earlier. The right of self determination entails the right to make decisions, including the choice to participate in a dangerous experimental trial. The fact that people participate in these studies does raise significant ethical questions. It may be the case that the poor can be

compelled by the need for money to participate in a clinical trial where most people of means would not.

I think that informed consent can answer many ethical questions, but in some instances, it raises more questions and concerns. I argue that informed consent does not mitigate the duty of the clinical researcher to protect the research subject from undue harm as a result of their participation in the study. Informed consent does not resolve all of the ethical dimensions of clinical experimentation. For one, it does not alleviate the possibility of coercion. There could be situations, where individuals are properly informed and consent, and yet the study in question is still not ethically permissible because they were coerced.

Consider the possibility that I am told of the risk involved in research and decide to decline to participate in the research. The researcher may then put a gun to my head and then tell me to sign the informed consent agreement. In the end, I participate in the research. Yet the clinical trial is not ethically permissible because my consent was obtained by force. The consent is not legitimate, because my right of self determination was violated. I was coerced and coercion, in most cases, is unethical.

Like many of the concepts we have already discussed, the concept of coercion is another of those often misunderstood notions found in the bioethical literature. Most recent philosophical discussion of the notion begins with an essay by Robert Nozick entitled, "Coercion".

In the essay Nozick employs the following analysis of the concept:

1. *P* aims to keep *Q* from choosing to perform action *A*;
2. *P* communicates a claim to *Q*;
3. *P*'s claim indicates that if *Q* performs *A*, then *P* will bring about some consequence that would make *Q*'s *A*-ing less desirable to *Q* than *Q*'s not *A*-ing;
4. *P*'s claim is credible to *Q*;
5. *Q* does not do *A*;
6. Part of *Q*'s reason for not doing *A* is to lessen the likelihood that *P* will bring about the consequence announced in (3) <sup>85</sup>

This argument applies to *P* coercing *Q* from acting but it also applies to cases where *P* coerces *Q* into acting. On this view if *Q* chooses to go forth and ignore the threat, then he has not been coerced. In most cases of coercion there is a threat of violence or harm. It can often involve a power relation, where one has authority over another. Although Nozick was primarily concerned with the concept as applied to political relations, it can be applied to case at hand.

The most brute example of coercion would be as follows: someone points a gun to your head and demands a specific action. As a rule, few, if any, clinical researchers do this- the Nazi doctors being a notable exception. Some argue that employing prisoners in clinical trials is unethical because the prisoners are in a coercive situation. I disagree. I think that there can be situations where it is ethically permissible to allow prisoners to participate as experimental subjects. I will not examine this issue in detail, but I would not arbitrarily rule out allowing prisoners to enroll in clinical trials. Yet coercion can take a myriad of forms, some of which are much more insidious. A recent example might serve to illustrate this point.

In 2004 South Korean Geneticist Dr. Hwang Woo-suk “pressured” (coerced) several female co-workers into “donating” their ovum for research. The process of harvesting eggs from a woman is very dangerous. Large amounts of hormones are employed, and the procedure for the extraction of the eggs can result in permanent sterilization of the experimental subject. An ethics board investigation concluded that he had used his position of authority to coerce female scientist to undergo the procedure. The board found that he threatened to terminate any female researcher that would not give him their ovum. In my view, this is clear cut case of coercion. These women were forced into research they otherwise would not have volunteered to participate in. On the other hand, if Woo-suk had simply offered a bonus, say \$10,000, to any of his co-workers that would undergo the procedure, then this would not have been a case of coercion. In the case where money is used as an incentive there is *no coercion*. In such an instance, women may feel compelled to undergo the procedure (because of the money) but they are not coerced. This view of coercion is not shared by the FDA. The FDA feels that money can be used to “coerce” or “unduly influenced” an individual; in my view it cannot.

In Title 21 Code of the Federal regulations chapter 50 part 20 it states in part, “An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”<sup>86</sup> What is meant by “coercion or undue influence” is not entirely clear. The FDA does allow compensation for participation in research,



but apparently there is a limit. Too much money, and in the FDA's view, the subject is either coerced or unduly influenced. The reality is that money, in most cases, is the central motivation for research participants to enroll in a clinical trial. This seems to be particularly true in cases where the research will provide no direct benefit for their condition or where they are a healthy volunteer.

I have argued that the right of self determination is a prima facie right of competent persons. It is part of the basis for our freedom and ability to make choices and take control of our life. Individual autonomy and the right of self determination, on my view, entails that individuals are at liberty to act in accordance with their beliefs and desires. One definition of liberty, employed by David Hume, is as follows: "*a power of acting or not acting, according to the determinations of the will*; that is, if we choose to remain at rest, we may; if we choose to move, we also may."<sup>87</sup> One interpretation of his views is that individuals are exercising their individual autonomy by being able to act according to the determinations of their own will. Our autonomy is not respected when others imposes their will upon our own. It is also violated, when someone else endeavors to make decisions for us. In the case of coercion, the threat of force is used. In the case of "compelling interest", some other means, be it rational argument or incentive is employed to sway our will. In cases where one is *not* forced by the researcher to participate, I do not see an ethical problem. It should not be ethically objectionable to endeavor to persuade someone, by means of rational argument to enroll in a clinical trial. It should be not more objectionable to offer them an incentive or inducement. The use of an incentive

or inducement to compel someone to participate in a clinical trial does not make their participation unethical.

In the case of clinical research our autonomy is respected when we are allowed to choose of our own volition to participate. In order to meet the requirement of informed consent, the researcher must provide the potential experimental subject with the pertinent information regarding the risk and benefits of participation, and the experimental subject thereby makes an informed choice. If the person is competent, and properly informed, then he has the capacity to make an autonomous decision. If he provides informed consent to participate (and are not coerced) then the research is ethically permissible.

The researcher respects the right of self determination by allowing competent persons to make the choice to enroll in clinical trials of their free accord. A person's rights and liberty can be violated in the following situations: If the researcher makes the choice for him, does not provide him with the requisite information, or coerces him into participating. In such cases the researcher has not respected his right of self determination or his autonomy. All of these actions, on the part of the researcher, are unethical.

In the first instance the researcher has not allowed him to make a choice. The physician has taken the decision out of his hands by simply enrolling him in the study regardless of his wishes. An example of this type is found in the Polyheme artificial blood clinical trial. In this clinical trial persons were employed as experimental subjects, in an extremely dangerous Randomized Control Trial, without their being informed of this fact or requesting their consent. I would

argue that their right to choose what is to be done with their person was violated because they were not given the choice to decide whether or not they wanted to enroll in the clinical trial. The researchers made this choice for them, in part, to further their own goals and ends.

In the second case, the researcher withholds or provides misleading information about the risk and the benefit inherent to the study. The experimental subject's autonomy and right of self determination have been violated because he made a decision to enroll in the research study under false pretenses. He was deceived into enrolling in the clinical trial. Perhaps, if the subject were told the true nature of the risk, he would not enroll in the study. In this case the subject believes he is making an informed decision, when, in fact, he is not. Deception on the part of the researcher violates the rights of the experimental subject. When an individual is deceived he is not able to make an informed decision.

In the final situation, the experimental subject is forced to participate in research that he would normally not enroll in otherwise. In this case the researcher says, enroll in this study or else I will inflict some harm upon you. In one sense, as Jean Paul Sartre pointed out in his 1943 book, Being and Nothingness, "man is condemned to be free". We are "free" even in coercive situations in the sense that we must make a choice. Even in this situation, we must make a decision. In the case of coercion, our autonomy has not been respected and our freedom or liberty has been violated.

Again if Dr. Hwang Woo-suk demands, "Give me your ovum or I will fire you from your research position", to one of his young lab assistants, the young lady is

still free to say “No. I will do no such thing”. Although he has attempted to coerce her into a particular decision, she can refuse the offer. In this case the young lady may weigh her options and determine that it is in her best interest to refuse the coercive demand. If freedom is simply acting in accordance with your beliefs and desires, then you are free. Yet in another sense the evil stem cell doctor has restricted your liberty, unjustly, by limiting your choices. In coercive situations this violation of our right to self determination and our personal liberty is unethical.

As Wilkinson and Moore point out, “Coercion is paradigmatically a case of the denial of autonomy, since it consist in the deliberate imposition of one person’s will one another.”<sup>88</sup> The doctor does not have a right to demand such a thing of the young woman. He has placed her in a situation where she must choose between the lesser of two evils, neither of which are justified. He has tried to force her into a situation where she must make a choice; a decision that she would not otherwise make. As stated above, her rights have been violated by his coercive demands upon her.

In most clinical trials coercion is not an issue. Potential test subjects come to the research site of their own free accord. They are not rounded up off of the street. The potential experimental subjects come to the research center, of their own free will and volition, with the intention of volunteering for a study. At no time are they forced to sign the informed consent document. The scientist is not strapping them down and forcing them to undergo procedures.

In my view, the motives of these individuals to undergo clinical experimentation and enroll in clinical trials are, for the most part, irrelevant to the question of the ethical permissibility of the research. In cases where competent individuals consent to participate in research, and are not coerced or forced by the researcher to do so, the clinical trials are, all things being equal, ethically permissible.

Money may be of compelling interest for many experimental subjects, and it may influence their choice to enroll in the clinical trial, but the researcher has not violated their rights or done anything unethical by offering them money for their participation. There is nothing ethically impermissible about paying research subjects, regardless of the amount. In the end, all of us feel compelled at some point in our lives to do things that we do not like, or we would rather not do.

As a poor graduate student I felt compelled by my economic circumstance to perform a job that I did not enjoy. I felt compelled to teach middle school mathematics for three years. The main impetus for my decision was the fact that I need to pay my bills. Regardless of my circumstances, I was not coerced. The principal did not hold a gun to my head or force me to accept the teaching position. The use of coercion, in all cases, makes the clinical research ethically impermissible. Fortunately, it involves a small minority of situations.

The FDA argues that inducement should not be so high as to “unduly influence” the test subject. The reality is that inducement is the only reason most people volunteer for phase 1 research. Most phase 1 trials involve testing novel compounds or reformulations of medications upon healthy volunteers to

determine their toxicity and potential side effects. Without some incentive, few, if any, people would consent to participate in such dangerous research. I argue that most of these trials do not involve coercion. Even though money is employed as a form of inducement in most phase 1 research, I do not believe that this entails that the practice is either coercive or unethical. On the other hand, there is the very real possibility that most phase 1 trials are exploitative in nature.

### **Exploitation**

There is one final consideration before we leave this discussion entirely: exploitation. Perhaps the poor are not “coerced” into participating in clinical trials, but rather they are exploited by the pharmaceutical corporations and clinical researchers. I will define exploitation as follows: A exploits B when A takes unfair advantage of B. What constitutes “unfair advantage” is rather contentious and certainly debatable.

In this context, one can consider the vast monetary gains received by the pharmaceutical companies for the products that are developed in clinical research, and the relatively minor gain to the participants of those trials and conclude that the practice is exploitative. There appears to be a great disparity in the gains made by pharmaceutical corporations as opposed to the minor gains (and great risk) of the experimental subjects used in their clinical trials. Given the disparity, *prima facie*, the circumstance appears, by definition, to be exploitative.

Even if we grant that some practices are exploitative, it does not follow that all exploitative practices are unethical or ethically impermissible. Consider the plight of the average college football player. The universities, television

networks, and college athletic conferences make a great deal of money from their efforts. Many of these young men sacrifice their bodies and futures for free or reduced college tuition. The disparity between their gain and the gain of the other parties involved seems to be very great. As such, the practice seems to be, *prima facie*, exploitative. Even so, does it follow that it is wrong?

In the case of college football players there is a risk inherent to such a dangerous and violent sport. Players suffer all sorts of injuries; some of them are quite serious. It is not unheard of for players to suffer concussions, break bones, suffer paralysis and on rare occasions, die. Clearly the risk can be very great. On the other hand, they are given scholarships. In some cases those can total \$50,000 dollars per year. They also have the opportunity to develop their skills and advance to the professional level. If this happens, they will be richly rewarded. In this instance, although the risk is great, the potential reward is also great. The disparity between risk and reward of the colleges and the athletes is not as great as it may first appear. The disparity does not seem to lead to an unethical circumstance.

It seems as though there is some sort of threshold that must be reached in order for an exploitative practice to be unethical. A minor disparity in the distribution of risk and rewards although exploitative may be ethically permissible, but a great disparity of the risk and rewards and the practice is unethical. As such, if the disparity between the risk and reward is too great, then one could argue that the participants have been exploited and, as a consequence of this, that the practice is unethical.

Most of the participants in phase 1 trials appear to be “exploited”. There seems to be a large disparity between the risk involved when one participates in some clinical trials and the potential benefit received. In some cases, such as phase one trials, there is no benefit at all for the experimental subject. According to FDA convention payment to the experimental subject is not supposed to be part of the risk benefit calculation for a clinical trial. What follows from this is unclear. If one argues that all exploitative practices are unethical, then we are left with the (absurd) consequence that all phase 1 trials are unethical. This seems to be false. Although there may be an “underclass” of poor individuals that systematically enroll in phase 1 research in the United States, it does not follow that the practice is unethical. As I have argued earlier, these persons have the right of self determination. It is their right to judge their choice of ends, and to choose, if they desire, to enroll as an experimental subjects. There is no reason for the government or some other agency to act paternalistically and infringe upon their basic right to participate in clinical research.

Another example might serve to highlight the distinction I am making. Recently BBC News ran a story about Iraqi woman that had immigrated to Iran and Syria. In the story many of the women interviewed explain how, because of their desperate economic circumstances, they had been forced into prostitution. One woman, a former university student, was asked if she ever imagined when she was at the university that she would end up being a prostitute. Her response was an indignant “Of course not!” but then she explained that, because of her



economic circumstances, this was the only means she had to provide for her family.

She stated that she could make more in one night of prostitution than humanitarian relief organizations would give her in a month. She made a choice, to sell her body, in order to provide for the needs of her family. Is she being exploited and yet at the same time making an autonomous decision? I believe the answer is yes. She is not being coerced. No one is forcing her to sell her body, rather she is making a free, autonomous decision; this is similar to the one that is made by people that enroll in clinical research. In a very real way clinical research subjects are selling their bodies to the pharmaceutical corporations. There is no reason to sugar coat this reality: one could argue that, as unsavory as this may sound, that they are prostituting themselves. Some might claim that this is unethical, both on the part of the individuals that participate in clinical trials and on the part of the pharmaceutical corporations that offer them; I, on the other hand, do not. I see it as a choice; it is a decision to sell their body, one they have the right to make.

As I have argued, we may grant that research subjects, especially in phase 1 trials, are exploited, nevertheless it does not follow that such a practice although exploitative is also unethical. Chris Elliot and Roberto Abadie claim that the way that clinical trials are currently conducted that they are “exploiting a research underclass”.<sup>89</sup> They argue that most phase 1 research conducted in the United States (and in Western societies) is exploitative of the poor. I am willing to grant

that it is, but I would argue that this does not entail that all of these trials are unethical.

In phase 1 clinical trials the majority of test subjects consent to experimentation because they are compensated financially. Prima facie, these subjects stand no chance of direct benefit from their participation in the research. Beyond this lack of benefit they stand a moderate to high probability of being harmed. In some cases they could be harmed severely. If you are willing provide your voluntary informed consent to a study that could be fatal for the sole purpose of financial gain, then I argue that this is within your rights to do so.

The notion of the individual autonomy of the person and the right of self determination entails the right to make decisions, including the choice to participate in a phase 1 clinical trial. As has been discussed already, it may be the case that the poor can be compelled, by the need for money, to participate in a clinical trial which most people of means would not. Some of the experimental subjects voluntarily participate in several trials each year in order to make a living. One could reasonably argue that it has developed into a form of work.

I have argued that enrolling in clinical trials, particularly those where there is no direct benefit beyond financial compensation, is analogous to work. In support of this thesis is the fact that many of us are compelled to take jobs that, all things being equal, we would rather not. Would you really want to serve in army in Iraq, if you had the ability or financial security to do something else? The army is, in some cases, offering a \$60,000 signing bonus for those individuals that volunteer for military service. This large amount of money will certainly compel

many young men and women to join the frontlines of war. Are they “coerced” into military service? I think the answer is no. Are experimental subjects “coerced” because they are paid to participate in research? I think the answer is no regardless of the amount of money they are paid. In both situations people find money to be of compelling interest to their decisions. The amount of money seems to be a significant factor that contributes to the decision to enlist or enroll.

This view is at odds with the FDA position. According to the FDA, “The IRB (Institutional Review Board) should review the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present an undue influence.”<sup>90</sup> <sup>91</sup> Again, I have argued that coercion, in most cases, involves a threat of some kind. I think that in order for an act to be an act of coercion, it must involve a threat of harm. This condition is not met when a person volunteers and is then paid for his participation in a clinical trial. The payment may serve as the experimental subject’s primary motivation for enrolling in the trial, but I do not view this as ethical objectionable.

The notion of “undue influence” does not seem to be as useful in regards to the ethical permissibility of clinical research as the FDA thinks. The FDA says that a bonus may be paid to subjects for completing a study. “A bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.”<sup>92</sup> I think that what the FDA has in mind is that subjects should not feel compelled to cover up side effects or remain in a clinical trial, where they would otherwise withdraw, because of financial incentives.

The reality, however, is that most of these subjects would not be participating in the clinical research, unless there was a financial incentive. In other words, compensation must be great enough so that subjects enroll in the research. If the compensation were set too low, then few, if any, subjects would be induced to participate in clinical research. It seems that any amount of compensation which influences persons to enroll in clinical research violates the standard of “undue influence”. If this is the case, then it seems pointless to discuss an “undue influence” because almost all clinical trials, where subjects are paid, seem to violate this standard.

If we consider compensation of any amount which is great enough to be a significant factor in an experimental subject’s enrolling in a clinical trial to be an “undue influence”, then any time a subject enrolls in a trial, and compensation was his primary reason, he has been “unduly influenced”. It seems all trials that offer compensation, do so to induce participation. Given the realities of phase 1 research, all trials, where subjects actually enroll, seem to violate this standard. Normally, one would not volunteer to enroll unless he was compensated in some way. Given that this seems to be the case, it seems that the standard of “undue influence” is meaningless. If, on the other hand, it is morally significant, then almost all phase 1 trials are unethical.

As I have said, I do not find payment of research subjects very problematic. My view is at odds with the dominant view in the literature that seems to find it ethically suspect. Most claim that it leads to exploitation of the poor. Although I hold a minority position, others share this position with me. Martin Wilkinson

and Andrew Moore have argued for financial compensation of experimental subjects.<sup>93</sup> Here is how they frame the question of payment. “Some researchers would find it worthwhile to pay inducements in order to attract enough subjects. Those who would accept this reward would not do so unless it was worth it to them. As a result of offering the reward, the researchers get the subjects they want. As a result of participating, the subjects get the reward they want. Both are better off. No one is worse off. Inducement is thus a good thing.”<sup>94</sup> Wilkinson and Moore note some of the arguments against inducement claim that “consent is invalidated by inducement.”<sup>95</sup> <sup>96</sup> Yet, as they note, many people perform tasks, under deplorable conditions, for money. “There is no suggestion in the vast majority of cases that their being paid undermines the voluntary nature of their actions.”<sup>97</sup> Consider once again the young Iraqi prostitute; her actions appear to be voluntary in nature.

I find payment to experimental subject no more objectionable than employing people to perform jobs that I, myself, would not take. Is a crab fisherman “coerced” because he is paid a percentage of the catch? Statistically, it is one of the most dangerous jobs in the world, yet, by the same token, it can be one of the highest paid. No doubt the adventurous crab fisherman in the Bering Straits may be influenced to take the job primarily because of the money, yet does the fact that money was the primary reason he took the job make the situation ethically suspect? Is it coercive or exploitative? I do not see how this is either coercive or exploitative.

On the other hand, if, while on a trip to Alaska, I am kidnapped and taken aboard a fishing boat and forced to work (with the threat of being thrown overboard), then I would say that this is an example of coercion (and slavery). If I am given the choice by my abductors to work or be thrown overboard, then I would rightly say I have been coerced into working on the boat.

Given the two cases, one where I volunteer to serve on the boat and the other where I am forced to do so, which is more analogous to the case of clinical research? I maintain that the case of voluntary consent is analogous to most research trials. In a case where an experimental subject has given his voluntary informed consent, then he has not been coerced. Coercion, as argued previously, involves a threat of harm or force on the part of the coercer. Normally, this is not the case in clinical trials.

Exploitation, on the other hand, can take place in situations where individuals have given their voluntary consent. Exploitation can take place when there is an unequal distribution of the risk and rewards. In the case of clinical research, the gains by most research subject, especially in phase 1 trials, are modest, as compared with the gains made by the pharmaceutical corporations. On the other hand, the risk and cost for the pharmaceutical corporations is minor, but the risk to experimental subject is potentially very great. It seems that there is only the potential for a modest gain by the research subject, but it comes at the risk of potentially great harm. There appears to be a great disparity between the risk and rewards between the pharmaceutical corporations and the research subjects. In some cases, the disparity is so great that the practice is unethical. Which trials are

unethical depends upon the risk and reward involved. One way to resolve this disparity between risk and reward would be to offer greater financial gains to experimental subjects.

The FDA opposes such a move, as they claim it would hold an “undue influence” over experimental subjects. They argue that it would compel test subjects to continue to participate in trials that may be too painful or dangerous for them to continue. As Elliot and Abadie argue, many subjects may fail to report side effects and suffer through a great deal of discomfort, because they want the modest financial gain they will receive as a result of completing the trial. Elliot and Abadie argue that the current inducement structure has resulted in a “torture economy” for those participating in phase 1 trials, as such; I would presume that they would oppose greater compensation for experimental subjects, as it would only serve to exacerbate the current situation. I, on the other hand, disagree.

If experimental subjects were compensated more, then the disparity between the risk and reward would be reduced, and the practice would be less exploitative. If it were less exploitative, then it would be more difficult for opponents to argue that it is unethical. As such, I would argue that phase 1 experimental subject should receive more, not less, compensation.

When most people think about compensation they assume that it must involve money, but there are various ways that research subjects could be compensated. The compensation to research subjects need not be money; it could just as easily be access to healthcare or pharmaceutical interventions developed as a result of

the research. Providing access to medical interventions that they help to develop by their participation in the clinical research might be more effective, an appeal to a large segment of the population, than simply paying money. It might be the case that they are “healthy”, and they do not need the intervention in question, now, but circumstances change. Perhaps in the future they will need it.

One might volunteer to participate in clinical research so long as he was guaranteed access to future medical interventions when they are approved. In such a situation, even relatively well off persons might volunteer to participate in phase 1 research. Given the exuberant cost of healthcare, if one were promised, contractually, the right to receive the purposed interventions that were developed, then many more people might volunteer to participate in clinical research. Perhaps, by enrolling in clinical trials with Pfizer, Merck or Bayer I could build up credit with them for future medication I, or my loved ones need. Such a system of clinical research does not seem the least bit exploitative.

As I said earlier, most of us will never volunteer to participate in clinical research, yet if the appropriate incentives were given many more of us would. In the end, a judgment must be made about how great exploitation must be for it to be unethical. I believe that there is some level, a threshold, where an exploitative practice becomes unethical. I think there are a number of trials conducted in developing countries where the disparity of risk and reward is so great, that the practice is at once both exploitative and unethical. On the other hand, I do not think that the same is true of most clinical trials conducted in developed societies.



## **Conclusion**

In this chapter I have argued against Kant's ethical theory as a foundation for patient/ experimental subject rights. I claim that each person has the right to determine for himself whether or not he will participate in clinical research. Our capacity to exercise our individual autonomy, our right of self determination, and our ability to give informed consent are sufficient to answer many of the ethical objections to clinical research. Clinical trials that respect our rights and that are conducted after obtaining informed consent are normally ethically permissible. It is the right of a person to determine what will and what will not be done to his person; if this right is employed as a foundation for clinical research then many of the ethical issues can be resolved.

Respect for individual autonomy does not answer all objections to clinical research, but it goes a long way towards resolving most of the issues. I have also argued against coercion in clinical trials, but I have maintained that not all forms of exploitation in clinical trials are necessarily unethical. Exploitation exists in a myriad of forms within our society. Ultimately our individual autonomy and our right of self determination will be used as a foundation for judging the ethical permissibility of research. Research that violates the individual autonomy and the right of self determination of persons is not ethically permissible. These notions will be applied to the diverse methodologies introduced in the preceding chapters. A consideration of paradigmatic cases of unethical research shows that the vast majority ignored the fundamental right of each person to decide whether or not to

participate in clinical research. Respect for our autonomy and our right of self determination requires that informed consent is obtained.

It seems clear that informed consent can be obtained in both principle (and practice) without one understanding all of the scientific principles or methodologies involved in the research study. I have argued for a moderate knowledge/understanding requirement in order to obtain informed consent. One need not be a scientist to give informed consent, but one should not be ignorant of what the research entails either. I believe that complex scientific methodologies can be explained in lay terms so that potential research subject can make an informed decision. So long as the potential test subject has a clear understanding of what will be done to his person, of the procedures involved in the study, and of the potential benefits and risk, then he should be able to give his informed consent.

Competent persons are at liberty to provide their informed consent to most clinical research. These ideas will be extended to specific types of research methodologies in the next chapter. Individuals have the right to choose to participate in a clinical study. Once persons have been informed about the risk and benefit involved with the research, then they can give their consent to participate in the research. Research that is conducted in accordance with these principles is normally ethically permissible.

### **Chapter 3: Therapeutic Obligation, Equipoise and the Ethical Permissibility of Randomized Control Trials with a Placebo Control**

In the realm of physical science, experiments are performed upon inanimate objects, the use of which hardly ever raises any moral objection. Once we venture to experiment upon humans however, a multitude of ethical questions arise. Unlike inanimate objects, persons have rights and clinical researchers have an obligation to respect those rights. The use of human beings as the objects of scientific inquiry and experimentation is open to ethical objection on several grounds; nevertheless it is my hope in this chapter to defend the ethical permissibility of clinical research and to defend the ethical permissibility of specific types of trials such as Randomized Control Trials (RCTs) and placebo control trials (PCTs). The arguments presented in the last chapter will be re-examined here; they will serve as the foundation for my ethical analysis and discussion of specific research methodologies.

One of the central concerns raised regarding the ethical permissibility of clinical trials involves the supposed therapeutic obligation of physicians and researchers. Clinical trials, in general, and RCTs, in particular, have been challenged ethically on the basis that a physician's therapeutic obligation to provide the patient with optimal care precludes enrolling them in clinical trials. The rationale for this claim is the idea that physicians cannot fulfill their therapeutic obligations to their patients by enrolling them in a study that involves an inferior treatment. It is claimed that clinical research that involves either randomization or a placebo control group leads to a patient receiving an inferior

treatment. It is argued that trials that employ these specific elements are usually ethically impermissible.

In the preceding chapter I defended the thesis that clinical research involving humans is normally ethically permissible so long as the rights of the experimental subject are not violated; specifically the right of self determination. I will engage in a further analysis of the ethical permissibility of clinical research. If my proceeding arguments in support of the ethical permissibility of clinical research are correct, then they will serve to support the ethical permissibility of specific types of clinical trials. I argue that most types of randomized trials, even those with the much maligned placebo control, are ethically permissible so long as the minimum requirement of informed consent is obtained from the experimental subject. I support the ethical permissibility of clinical trials so long as they do not violate the rights of experimental subjects. I propose a minimalist approach when it comes to the ethical permissibility of clinical trials. Instead of a plethora of ethical requirements and regulations, I have argued that competent individuals have a right, the right of self determination, to exercise their autonomy and give their informed consent to participate in clinical research. Most clinical trials are ethically permissible if they meet the following conditions:

- 1) The potential experimental subject is competent to exercise his autonomy and his right of self determination in order to enroll in the trial.
- 2) The potential experimental subject is adequately informed about the nature of risk and benefit involved in his participation in the clinical trial and provides their voluntary informed consent.
- 3) The trial employs a scientifically/ epistemically valid methodology and/or design.

4) The trial investigates a scientific question or questions of merit or importance.

The clinical researcher must respect the right of self determination of all potential experimental subjects over their own body and person. The researcher must allow each potential experimental subject the opportunity to choose to participate in a clinical trial of his or her own accord. Further the clinical trial must be conducted only after obtaining informed consent. The research must not employ fraud or deception in order to obtain consent. In such a case, the consent is not “informed” and the research is unethical. Further, it is necessary that the researcher employ a scientifically valid methodology. It is unethical to risk harm to experimental subject in trials that are methodologically flawed. Finally, the trial should investigate an important scientific question. It is unethical to risk harm to persons to answer trivial or unimportant questions.

Respect for right of self determination (our capacity to exercise our individual autonomy regarding our choice of goals) and informed consent has been defended by others.<sup>98</sup> These two principles taken together serve as foundation for most codes of research ethics. These principles are essential for ethical research according to the Tri-Council of Canada. The Tri-Council of Canada represents the views of three Canadian organizations regarding research ethics. The Tri-Council is made up of the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada. The Tri-Council policy statement is contained in the document entitled, “Ethical Conduct for research Involving Humans”.

The Tri-Council states document states in part:

The cardinal principle of modern research ethics is respect for human dignity. This principle aspires to protect the multiple and interdependent interest of the person- from bodily to psychological to cultural integrity. This principle forms the basis of the ethical obligations in research... Individuals are generally presumed to have the capacity and right to make free and informed decisions. Respect for persons thus means respecting the exercise of individual consent.<sup>99</sup>

These same principles are found in various statements of moral codes. From the Nuremberg Code to the Declaration of Helsinki respect for the individual is of paramount importance. These codes serve as a foundation for the discussion of the ethics of clinical research, but are not (as some writers believe) the final word. I will reference different moral codes from time to time, yet I will conduct a philosophical analysis of their importance and their relation to the ethical permissibility of clinical research in a subsequent chapters.

I will examine the ethical permissibility of specific types of clinical designs in light of the principles of right of self determination and informed consent that I defended in the previous chapter. The clinical trials to be considered include historical trials, observational studies, and Randomized Control Trials (RCTs). RCTs are by far the most discussed type of trial design in recent literature and the RCT with a placebo control (PCT) the most controversial.

I defend the ethical permissibility of both RCTs and PCTs. It has been argued that these trials are unethical because they violate the physician's therapeutic obligation to his patients. I will examine the notion of therapeutic obligation and argue that it does not preclude a physician offering to his patients the option of enrolling in clinical trials. This discussion will then lead into an analysis of

clinical equipoise, the role of the physician (clinical care) as opposed to the clinical researcher (clinical research). The chapter will conclude an analysis and defense of the minimum necessary conditions for ethically permissible of clinical research that have been stated at the outset.

**Necessary Conditions for Ethically Permissible Research: The Capacity to Exercise Our Autonomy, the Right of Self Determination, and Informed Consent**

I defend a minimalist approach to evaluating the ethical permissibility of clinical trials. I feel that most clinical trials are ethically permissible of so long as certain conditions are met. Each competent person has a right a prima facie right of self determination. Each of us has the right, the liberty and freedom to decide for ourselves what we want to do with our lives. When others impose their will upon our own (even if they do so for beneficent motives) they violate our right of self determination. In my view the most important condition for the ethical permissibility of any clinical trial is that the right of self determination of competent individuals is respected. It is my view that respect for right of self determination is a necessary condition for ethical research. The autonomy of competent individuals entails certain rights. The rights of each research subject entail certain obligations for the clinical researcher. It is more robust than what is often termed “respect” in the literature.

Another necessary condition (where it is possible to obtain) is informed consent. Individuals must be competent to give their informed consent. This condition assumes that they understand, in general terms, the nature and the risk of the clinical research they are consenting to participate in. Taken together the

right of self determination of persons and their ability to provide informed consent (in most cases) are necessary and sufficient in normal circumstances for scientifically valid clinical research to be ethically permissible. If the research methodology is believed with good reason to not be scientifically valid then it is unethical to recruit subjects to participate- even if they are willing to consent. Miller, Emmanuel and others have argued that, “Scientific validity is an essential ethical requirement of clinical research. No person should be subjected to the risks of research participation in studies that lack scientific validity.”<sup>100 101</sup> This view may be too strong, but it would seem unreasonable to enroll subjects into trials that are not scientifically valid. The validity of diverse research methodologies is in dispute.

Previously I have argued that RCTs and PCTs are both the optimal clinical design and epistemically necessary to confirm the efficacy of most medical interventions, but that does not preclude the use of other lesser research methodologies if their use is warranted for ethical reasons. In either case, whether we hold a strong or weak validity requirement, this may have important implications for some of the research methodologies, specifically designs that have been shown to yield unreliable, biased or invalid data. If a research methodology is epistemically flawed then it ought not to be employed.

### **Types of Clinical Trials**

As stated in chapter 1, there are many types of experimental design. Some of the most prevalent types of experimental design include: Historical Control Trials (HCT) - sometimes termed observational studies, Randomized Control Trials



(RCT), Active Control Trials (ACT), Pre- Randomized Control Trials (pre-RCT), and Placebo Control Trials (PCT). I have argued that clinical research is normally ethically permissible so long as the right of self determination of experimental subjects is not violated and they have given their informed consent to participate.

Although I have defended the position that clinical trials are normally ethically permissible given certain condition are met, many of these design methodologies have been criticized on ethical grounds for various reasons. I have adopted a minimalist approach to the evaluation of the ethical permissibility of clinical research. On my view most clinical research is ethically permissible, so long as the experimental subject's right of self determination is not violated. This view is at odds with the current norm in clinical research. In order to defend my position, I will analyze several different research methodologies.

### **Ethical Analysis of Historical Control Trials**

In a Historical Control Trail, HCT, there is no randomization, no blinding, and no control. These trials are often termed “observational studies”. As a stipulative definition, I will employ the term Historical Control trial or HCT to refer to those trials that are comparative studies, conducted by examining historical patient records, in order to collect data. “In a clinical trial using historical controls, control data are derived from the experience of the institution with treatment of the disease in question accumulated before the introduction of a new therapy.”<sup>102</sup>

The scientific validity of these trials was called into question in chapter 1. If that conclusion is true, then one may call into question the ethical permissibility of these trials since they put people at risk by employing an unsound research

methodology. Normally the purpose of clinical research is to test the efficacy of an intervention. None of the trials to be considered, except RCTs, can do this effectively. If this is true, then it would seem absurd to recruit people to participate in potential research that ultimately cannot answer the proposed hypothesis.

It has been argued by proponents of this position that only PCTs can provide assay sensitivity, whereas other inferior designs cannot. If this true, (and I must admit that this point is contentious), then it would seem unethical to employ humans as subject in experiments that will, in principle, yield invalid results or at best yield results that cannot confirm the efficacy of the intervention under consideration. If this is the case, more testing will be required, which, in turn, will result in more experimentation and potential harm to experimental subjects. It also means that more people will suffer longer with ineffective medical interventions, as they have not been properly tested or confirmed.

Doesn't it make more sense, wherever it is possible, to employ an experimental methodology that can answer the question of efficacy and limit the number of test subjects required in order to do so? In other words, why risk harm to research subject if the trial cannot answer, at least in principle, the proposed hypothesis? It is an unnecessary expense of resources. Further, it is a violation of the rights of persons to place them in harm's way if the research methodology employed is not sound. There is no good reason to risk harm to the experimental subject if the experimental cannot provide a generalizable result. It is unethical to

employ subjects in experiments that cannot, in principle, answer the medical intervention under consideration.

As we consider the ethical permissibility of HCTs, let's work under the assumption that such trials can be employed to serve as the basis for scientifically valid conclusions. For the sake of argument, let us assume that above criticism does not hold, and for the time being, leave these objections aside. Even so, there are still several ethical concerns that can be raised regarding this type of research methodology.

Most HCTs are conducted after a treatment has been given to the patients. If a patient's confidential medical record is going to be employed then his consent ought to be obtained. I would argue that these trials are normally unethical unless that condition is met. Prima facie, if it is the physician's intent to conduct research and collect data from his patients for future study, then the patients should be made aware of this and their informed consent should be obtained. They should be informed that data will be collected and used to conduct medical research.

In HCTs two groups of patients are usually compared in order to evaluate the effectiveness of various therapeutic interventions. In a situation where patients are receiving a new treatment, they should be informed of this. They should be informed that the treatment is new, novel or not the standard of care. By the same token, patients that are provided with the standard treatment should be informed that there exist a new, novel and perhaps innovative treatment option as opposed to just standard care. All patients should be consulted and ought to be made aware of all of their treatment options. Respect for persons and the notion of right

of self determination, necessitate that patients have a choice in the course of their medical care and treatment.

Others might challenge the ethical permissibility of giving treatment to patients with the intent of later employing the results in a research study.

Theoretically, as a practicing physician, I could give the first two dozen patients I see with a particular condition treatment X. I could then, within the setting and context of clinical care provide the next two dozen patients with the same condition treatment Y. In the end I could collect the data for use in a HCT.

In this hypothetical case I am clearly conducting a clinical experiment, but I am not respecting right of self determination nor am I obtaining informed consent. In this instance, I have not even told the patients what I am doing. In such a situation, as a physician I have violated my patients' rights and the principle of informed consent by conducting research upon them without their knowledge or consent.

It is possible, in the context of clinical care, that physicians could randomize and blind their patients without their knowledge or consent. Such practices, at the minimum violate the prima facie right of self determination which is enjoyed by all competent persons. It violates this right by ignoring the patient's capacity to act autonomously. It is also unethical because both the physician and clinical researcher have an obligation to obtain the informed consent of the research subject; failure to do so is unethical. Research conducted in this manner, which ignores the right of self determination and the basic principles of autonomy and informed consent is clearly unethical (regardless of the results).

I am not suggesting that all historical trials are conducted in this way, but the fact that they could be, ought to make them, *prima facie* ethically suspect. In general, most writers do not view these studies as very controversial. I, on the other hand, do see the potential for ethical objections and concerns. My final point is this: all studies involving human subjects ought to be critically examined for their scientific validity and their ethical permissibility. All types of clinical research, even those which on the surface seem rather boring or mundane, raise significant moral questions. The ethics of HCTs and observational studies has been overlooked in recent years as people have debated the use of RCTs.

### **Ethical Analysis of Three Common Types of Observational Studies**

The above considerations may be applied to most “observational studies”. These concerns may legitimately be raised to the three main types of observational studies: the cohort design, the case-control design and the cross sectional design.<sup>103</sup> The differences between these designs were discussed in chapter 1. Once again, I will point out that if the patient’s confidential records are going to be used, then his consent must be obtained. He should be told that the results of his treatment will be used for further study. Beyond this, at a minimum, the patient’s right of self determination must be respected; in order to respect this right, his informed consent must be obtained before his records are used.

The main ethical concern I see with these studies (assuming they are conducted by simply reviewing medical records long after treatment has been administered) is that consent from the patient to use his or her medical records for research ought to be obtained. In a situation where one is conducting a HCT or

observational study involving current patients, the concerns noted above make such a research practice ethically suspect. Theoretically, a practicing physician could conduct an experiment upon current patients by simply breaking them into groups and prescribing them different medications. Although this “research” is being performed, it is being done on unwilling and unknowing volunteers. This may happen in clinical practice, but when it does, it is unethical. The physician should be endeavoring to treat his patients, not conduct clinical research upon them.

In cases where patients cannot give their permission for their record to be used to conduct research, (this certainly cannot happen in studies where the end point is death), then their legal representative ought to give their permission for the records to be used. Privacy and confidentiality is another aspect of clinical research that is sometimes overlooked. A patient’s chart may be filled with titillating and embarrassing details. When conducting a HCT, researchers will be pouring over this private information. This is another reason why the patient’s permission ought to be obtained before such research is conducted.

The points made regarding HCTs still have bearing upon these types of studies. Within the context of clinical care, the physician must focus on treating patients with what he thinks will be the optimal therapy for their condition. In an instance where the standard treatment is ineffective he may then recommend novel or experimental therapies to his patients without worrying about violating his therapeutic obligation. On the other hand, in situations where a physician is using patients for research, their right of self determination and their autonomy

must be respected; this requires that their informed consent be obtained before they are employed as experimental subjects.

Before we leave HCTs altogether, let us consider an example. If I want to ascertain the effectiveness of penicillin in the treatment of urinary tract infection as opposed to Zithromax, I may have to examine fifty years worth of patient records before I have enough cases with which to make a statistically significant comparison. If the records are very old it may be the case that many of these patients have moved or are deceased. There may be no effective way to contact them or their legal representatives.

In this specific case, within this context, I'm not sure what harm, if any, could befall the patients. I think that such a "trial" does not raise any significant ethical concerns. If precautions were taken to protect confidential patient information, I would not entertain any ethical objections to conducting such a study. This case is significantly different from a case involving the records of current patients. With current patients a different set of ethical concerns and objections may legitimately be raised.

### **Ethical Analysis of Randomized Control Trials**

As has been previously stated, there are various types of RCTs. The types include Active Control Trials (ACT), Pre- Randomized Control Trials (pre-RCT), and Placebo Control Trials (PCT). There are various ethical considerations raised by specific features of RCTs.

**TABLE 3.1- Types of Randomized Trials**

<b>Randomized Control Trials (RCT)</b>	<b>Randomized Control Trials (RCT):</b> In a Randomized Control Trial, RCT, patients are randomly placed into one of the treatment arms.
<b>Active Control Trials (ACT)</b>	Randomized, comparative studies of two or more therapeutic interventions.
<b>Pre Randomized Control Trials (pre-RCT)</b>	Subjects are placed into one treatment arm and then asked to consent to the therapy. No blinding. In some cases patients receiving the standard treatment are not asked for Informed Consent. Proposed and defended by Marvin Zelen. <sup>104</sup> This study design was employed with neonates as the study participants. Several infants died during the course of this research. This specific case will be considered at a later juncture. <sup>105</sup>
<b>Placebo Control Trials (PCT)</b>	Randomized, blinded with a therapy compared to a placebo control group. Patients are randomly assigned to either the experimental treatment arm or the placebo arm of the study. These types of trials may include double blinding; they may also have multiple treatment arms.

In a Randomized Control Trial, RCT, patients are randomly placed into one of the treatment arms. This is done in order to avoid, in theory, selection bias. Let us consider the ethical permissibility of randomization specifically before we consider the myriad of types of randomized trials. It has been argued that the



physician's therapeutic obligation towards his patient entails that he must prescribe the optimal treatment. As such, it has been argued, that prima facie, a physician acts unethically when he recommends that his patients participate in Randomized Control Trials- especially trials involving what the physician consider to be inferior treatments. This criticism assumes that the obligations of clinical practice (or clinical care, I use the terms synonymously) are the same as those found in clinical research. I defend the thesis that they are not. Those that oppose physicians enrolling patients in RCTs assume that the standard treatment is effective for the patient in question. The reality is that although there are standard treatments for a myriad of ailments, not all standard treatments work for all patients. There are plenty of standard treatments that are ineffective for particular patients; given this reality, it might be reasonable for a physician to suggest to his patient that he enroll in a clinical trial.

Many opponents of RCTs and PCTs maintain that if a doctor has a therapeutic obligation to, among other things, provide his patient with optimal care, then suggesting that a patient participate in a RCT, where the treatment is chosen by a randomization mechanism is always unethical. My point is this: it may not be. It is not always unethical for a physician to recommend that his patient enroll in a RCT. Even if we were to accept that physicians have a therapeutic obligation, and that such an obligation requires that they provide their patients with an optimal treatment. Randomization is considered unethical by many opponents of RCTs because a patient could end up receiving an inferior treatment, yet this assumes that the standard treatment actually works. The reality is that it may not

work; enrolling in a RCT or a PCT may be of equal ameliorative value as the standard treatment for some patients. It may be of equal ameliorative value because the standard treatment may not work for the patient. If the patient has already tried the standard therapy, and it has failed, then there is no morally significant reason as to why they should not consider participating in a RCT or PCT.

It is true that the use of randomization could result in patients receiving a sub-optimal treatment if they are randomized into an arm of the study that contains such a treatment, but this assumes that the standard treatment is effective for the patient. It also assumes that the patient cannot reasonably choose a therapy that is not the standard of care- which I deny. Another way this issue can be resolved is if the efficacy of the standard treatment and the treatment under consideration is unknown (assuming there is no third best treatment alternative that is superior to the other two) or if one treatment is no better than the other. If the treatments are known to be of equal ameliorative value then there is a state of equipoise. Some argue that a state of equipoise is necessary for an RCT or PCT to be ethically permissible; once again I do not believe that this is a necessary condition for the ethical permissibility of an RCT or PCT. I will examine the notion of equipoise in detail below beginning on page 146.

In my view, randomization, within the context of clinical research, does not raise a serious ethical problem so long as the patient understands what this entails. Within the context of clinical care, it is akin to the physician flipping a coin with treatment options. This seems to be unethical- unless the treatments are

approximately equivalent. As I have argued, the patient has the right to enroll in a clinical trial that involves the possibility of receiving a sub-optimal treatment, but why would he choose to enroll?

Many commentators assume that it is unethical for a physician to ask his patient to enroll in a RCT or a PCT. The underlying idea is that the physician should offer the patient the standard of care, yet it is also assumed that the standard of care is effective for the patient. The reality is that for many medical conditions, the standard treatment is ineffective for the vast majority of patients. Since the standard treatment may not work for a particular patient, it might be entirely reasonable for the patient to enroll in a clinical trial testing a new treatment. Even if the trial has a placebo control arm, patients still stand the chance of receiving some treatment. Even though the treatment, as yet, has not been demonstrated to be effective, it is better than receiving an approved, but ineffective standard treatment. In cases where the standard treatment is ineffective or there is no standard treatment then no ethical objection should be raised to a physician that suggests that his patient enroll in a clinical trial.

In many cases there is an optimal course of care, and the physician ought to recommend it. If the standard therapy is effective then the physician *should not* recommend that his patients enroll in a clinical trial. Yet if the standard of care is ineffective then the physician ought to explore other options for care. Those options should include experimental therapies and clinical research. Ultimately it is my position that if the patient is informed and consents to participate in a

clinical trial, then he is at liberty to do so. The physician ought to respect the patient's decisions in almost all cases.

Can a physician respect the right of self determination of their patients and at the same time refuse to provide the therapy that they request? If the doctor does not feel comfortable with the patient's decision then I would argue that the physician (on the basis of his professional obligation) may request that the patient seek another practitioner. If the doctor feels, in his considered medical judgment, that the requested treatment is too dangerous or will not be efficacious for a particular patient then he may justly refuse to provide or participate in the patient's treatment.

In this context the physician's rights and their professional judgment ought to take precedent over the patient's demands. By the same token, the physician cannot rightly force the patient to seek treatment, yet neither is he required to participate in course of treatment that he does not feel will work. In the end, if the patient disagrees with the doctor he or she is free to seek another professional opinion, and to attempt to find treatment elsewhere. The physician's professional obligation and the principle of care must take precedent over his personal values. In my mind, this conflict of rights and values is a nonstarter. Imagine a case where a patient, Jim, comes into the doctor's office demanding the latest pharmaceutical intervention he saw advertised on TV. The drug can be used for a class of patients with Jim's condition but the doctor does not think, in his professional judgment, it is appropriate for Jim. Does respect for Jim's rights entail that the doctor should prescribe it anyway?

This is an interesting case for several reasons. For one, given the nature of pharmaceutical advertising in the USA, it is reasonable to assume that this is a common occurrence in doctor's offices across America. I have no doubt that this situation plays itself out daily. In this case the doctor ought to explain the reasons for his reservations to the patient. The physician should explain why he does not believe that it is appropriate for Jim's case.

The explanation should also include a rationale as to why he thinks that Jim's current medication is superior to the new drug. In the end should the patient have the final decision as to what medication he will use? Would this be consistent with the notion of the right of self determination and physician obligations that I have employed? I feel that if the physician is adamant, (based upon his professional knowledge), that the new drug is not appropriate or may even be harmful to the patient then he has an obligation to refuse to prescribe it to the patient. He is not obligated to participate in a treatment that he does not feel, in his professional judgment, is appropriate for the patient. In this situation the patient's rights are not violated; they are at liberty to seek treatment elsewhere. In such a case the rights of both the patient and the physician have been respected. In a case where giving in to the patient's demands will result in harm, the physician may, ethically, refuse to do so.

In the end, this entire situation is purely speculative. It is hypothetical because long before Jim came in demanding the new drug, the pharmaceutical companies have already wined and dined the physician, given him lots of free samples, and have asked him to prescribe their new wonder drug as often as possible. (One

might ask whether these practices are compatible with the principle of clinical care.) This is a separate issue, but as many opponents of clinical trials insist upon employing the notion of therapeutic obligation, I will point them in a direction with which to apply that notion- to a case where it actually holds.

I'd like to return to the discussion of RCTs. If all of the patients involved in the study are receiving some form of treatment then they are participating in an Active Control Trial, (ACT). In ACTs patients are randomized into different treatments; thereby comparing one treatment against another. In the case of ACTs, where the trial is comparing two or more treatments, it is argued that the doctor violates the principle of care or therapeutic obligation if he feels that one treatment is superior to another. It has been argued that he violates his therapeutic obligation if he allows his patient to enroll in the inferior arm of the trial.

One solution to this problem is the notion of equipoise. One interpretation of this term is that "equipoise" holds between two interventions if, and only if, there is "credible doubt" about their "relative therapeutic advantage and there is no third intervention that is preferable to at least one of them."<sup>106</sup> If a physician is in a state of equipoise regarding the efficacy of two or more treatments then, he does not know which treatment is better. In this case it is believed that both treatments are equal, or that there is no reason to prefer one above the other.

In this instance it is claimed that randomization is not of ethical concern because both treatments are on equal footing, neither is inferior. The doctor fulfills his therapeutic obligation because he is not prescribing an inferior treatment. Regardless of what arm of the study a patient is randomized into he

will be receiving some treatment. The physician fulfills his therapeutic obligation because he does *not* feel that there is an inferior arm of the study; he considers both arms of the study to be equivalent in treating the patient's condition.

In a Pre-Randomization Clinical Trial experimental subjects are placed into one treatment arm and then asked to consent to the therapy. There is no blinding because patients that are randomized to the standard treatment arm are not told there is an alternative experimental treatment. However, patients randomized to the experimental treatment are told it is experimental and asked to sign an informed consent agreement. In most cases patients receiving the standard treatment are not asked for informed consent nor are they told that they are being used in a RCT. This trial design has been proposed and defended by Marvin Zelen.<sup>107</sup> This type of trial has been run in a number of cases. In my view all of these trials were unethical because they violated the rights of the experimental subjects as informed consent was not obtained. Persons were used as experimental subjects without their knowledge or consent.

Although there is near unanimous consensus that informed consent is a necessary condition of clinical experimentation, some aspects of informed consent remain controversial. Some argue that you do not need to obtain consent from a patient that is receiving "standard therapy". This is the case in the Pre-RCT or randomized consent design for clinical trials as proposed by Zelen. This design permits doctors to randomize patients without consent. The physician then obtains informed consent from only those patients randomized to the experimental arm. Patients randomized to the standard treatment arm are not told that they are

participating in a clinical trial. They are not told that there is an alternative therapy. Finally they are not asked to provide their informed consent. All of these conditions violate their right of self determination.

There are a number of ethical concerns that can be raised to this type of clinical trial design. First and foremost, it is a violation of the prima facie right of self determination of competent persons. I have argued that every competent person has a right and the capacity to exercise his individual autonomy to enroll them in research. One cannot do this if they are not privy to or even aware of the clinical trial. This type of design is reminiscent of the darkest days of clinical research, from Tuskegee to Nazi death camps. A physician should not randomize patients into an arm of a clinical trial and not tell them that this has been done. The use of this trial design is morally reprehensible. This type of research also violates the clinical care principle as discussed above. Beyond this, even if this sort of trial were employed in the setting of clinical research, a cohort of subjects, would still not be informed that randomization had decided the course of their treatment. In my view this design is clearly unethical and should not be employed. It should be avoided at all cost.

In support of my position, consider a clinical trial that employed this design. The study involved newborns that were diagnosed with persistent pulmonary hypertension (PPHN). In the late 70's and early 80's the death rate for newborns with this condition was approximately 80%. In 1977 R.H. Bartlett conducted a RCT at the University of Michigan with an experimental therapy known as extracorporeal membrane oxygenation (ECMO). The survival rate of newborns



treated with ECMO was over 80%. The trial used a special “play the winner design” so that only 1 infant ended up in the control group. The infant in the control group, which received standard treatment died. The other 9 infants, that received the experimental therapy, survived. Commentators argued that because only one child received standard therapy, the efficacy of ECMO was not confirmed by this trial.<sup>108</sup>

In 1985 a second trial was conducted by James Ware at Harvard University employing Zelen’s Pre-RCT design. 10 infants were assigned to the control side. 4 of those 10 newborns in the control group died. The Pre-RCT design does not require informed consent for patients who receive conventional therapy. Since these infants were randomized to the control, and were given conventional therapy, their parents were not told they were to be used in a study, nor their informed consent obtained. The parents were not informed that there was a promising alternative to conventional therapy. Ware claims that he strived “to balance ethical and scientific concerns...”<sup>109</sup> yet I would argue that he violated the rights of the infants that were employed in this. 40% of the babies assigned to the control group died, more died in future trials. This trial should never have been conducted in the first place. Trials of this type, conducted without informed consent are analogous to the experiments conducted in the Nazi concentration camps. How can a doctor justify *not* informing the parents involved that there is a promising new therapy that could save their child’s life?

In criticism of Ware's methods Richard Royall says:

Zelen's randomized consent procedure produced a situation in which parents of a critically ill infant, for whom conventional therapy held little hope of survival were not even informed that a highly promising alternative therapy was available for their baby, but by chance (the randomization procedure) conventional therapy had been selected instead. Would they have chosen to let their baby remain in the study and receive conventional therapy, if they had been given the information and the choice? <sup>110</sup>

Unfortunately, we can never know what choice the parents would have made, but we can assume that they would have requested the experimental therapy.

As a result of ECMO many infants were saved, but at what cost? The pre-randomized design was used because it was felt the parents would have a preference for the new therapy over conventional, thereby making it impossible for a statistical significant number of patients to enroll in the control side of the trail. Obviously given the choice of an 80% death rate with conventional therapy and an 80% success rate with the alternative, parent would have selected the alternative. This raises another issue, one discussed in the first chapter: must RCTs always be employed to confirm the efficacy of an intervention? The short answer is no. There are certain, rare cases where the preponderance of evidence gleaned from observation or other sorts of experimental methodologies is so great that one need not confirm the efficacy of a medical intervention with a RCT. Kazdin and Erwin have considered such cases. One simple example where an RCT would not have been necessary to confirm efficacy would be the dramatic effect that introduction of penicillin had upon various diseases. The discovery of a drug like penicillin is extremely rare. Normally the statistical difference

between an efficacious medical intervention and an ineffective medical intervention is very small. In other words, the results are not very dramatic. Normally a RCT will be the only way to confirm the efficacy. Although RCTs are of great epistemic importance, it does not follow that it is ethical to run a RCT in all cases.

There will be times when it will not be possible to conduct a RCT, ACT or PCT because people will not be willing to risk receiving a dangerous new therapy or an inferior conventional one. Respect for the right of self determination and the autonomy of persons requires that trials like the Harvard ECMO study are never conducted again. As Marcia Angell points out, “It simply may not be ethically possible to conduct a valid Randomized Control Trial under these circumstances. {Where there is a vastly superior treatment or patient’s lives are in danger}”<sup>111</sup>

The research mentioned above brings into focus what I would term “the starting problem”. The starting problem can be stated as follows: in certain rare cases it is not possible to conduct ethically permissible RCTs. In cases such as the Harvard ECMO trial a RCT should not be employed. In such cases RCTs should not be used. If possible an alternative type of trial can be employed. It is possible that an ACT could be used, or, even with all of its epistemological flaws, an observational study. I think that the Pre-RCT is a fundamentally unethical. It is a design that co-ops patients into being research subjects, and ignores the fundamental tenets of respect for the rights of persons and their informed consent; these features are the minimum requirements of ethically permissible research.

Most of the ethical controversy involving RCTs is regarding the ethical permissibility of Placebo Control Trials, PCTs. In the case of PCTs, there is the possibility that a patient will receive no treatment. Since no treatment, cannot be the best treatment, any doctor that enrolls a patient in a PCT is said to violate both the right of the patient to receive optimal care and his therapeutic obligation to the patient. In the case of a PCT, equipoise is of no help, unless the doctor is convinced that the standard treatment is ineffective or that the standard therapy is no more effective than a placebo. Whether or not equipoise can resolve this problem will be considered in this chapter, but opponents of such trials claim that there is an inherent conflict between the use of RCTs, specifically PCTs and therapeutic obligation. Again most critics claim that PCTs are unethical because they violate the right of the patient to receive optimal care and the physician's duty of therapeutic obligation to provide that care.

Many opponents of PCTs assume two things, 1) that patients have a right to receive optimal care and, 2) that physicians have a therapeutic obligation. From this they claim that it follows that it is unethical to enroll patients in trials involving inferior treatments. I disagree with this conclusion. Even if we grant that patients have such a right and that physicians have a corresponding obligation, it does not follow that it is unethical to enroll patients in clinical research in most or all cases. It is ethical, if patients decide to enroll of their own free accord.

### **Clinical Care and Clinical Research**

I argue that the role of a physician is different, in a morally relevant way, from than that of a clinical researcher. The clinical researcher and the physician stand in different relations and have different duties to patients and test subjects respectively. Even if we concede that doctors do have a therapeutic obligation to see that their patients receive optimal care it does not follow that the clinical researcher is bound by the same therapeutic obligation. The clinical researcher serves a different function, is motivated by different goals, and stands in a different relation with the test subject than a physician does to a patient.

The clinical researcher is not bound by a therapeutic obligation to see that a given patient is given the optimal treatment. The clinical research has several ethical obligations to the test subject, but a therapeutic obligation is not one of them. The researcher has an obligation to inform the experimental subject of the risk and benefit involved in clinical research. He has an obligation to respect the experimental subject's right of self determination and has an obligation to obtain informed consent from the experimental subject.

The distinction between the role of a clinical research and a physician might seem like a minor point, but given the structure and nature of FDA endorsed research, there are several morally relevant differences between seeing a patient in a therapeutic setting and meeting one in the setting of clinical research. If those boundaries are clearly defined, then this issue that therapeutic obligation is not being fulfilled by the clinical researcher, in my estimation, can be avoided. This criticism simply does not apply within the context of clinical research.

The case becomes more clouded when those boundaries are obscured. A similar point has been made by others, regarding the decisions that are made by physicians within the setting of their practices. In a controversial article entitled, “Is Informed Consent Always Necessary for Randomized, Control Trials” Robert Truog and Walter Robinson point out that in the context of clinical care a physician could conduct an experiment without any oversight (from the FDA or an IRB) or the knowledge of his patients.

As Truog and Robinson point out:

Consider the paradox: if a physician reads a case report about novel method of ventilation for critical ill patients and wants to try it in the next several patients with respiratory failure he or she treats, the physician may do so provided the patients have given general consent for treatment. On the other hand, if a physician is interested in performing a randomized, control trial to determine rigorously which of two widely used antibiotics is more effective at treating bronchitis, he or she must prepare a formal protocol, obtain approval from the institution review board, and seek written informed consent from potential patients. In each case the physician is performing an experiment. In each case, there is uncertainty about the best way to treat the patient.<sup>112</sup>

To conduct an impromptu clinical trial in this manner is unethical. Just because it is the case that a physician can do this, does not mean that he ought to. Simply because a physician could manage to do this, given the current regulatory structure, it does not follow that it is ethical. In fact, this sort of experimentation ought to be avoided at all cost. It violates the right of persons, including the right of self determination of the patient, and in the context of clinical care, it is a violation of the physician’s therapeutic obligation to his patients. I will examine the notion of therapeutic obligation in more detail in a moment, but I will say that

within the setting of clinical care, the patient's interest must, all things being equal, be served above all else.

The preceding example by Truog and Robinson illustrates the problem with differentiating clinical care from clinical research when it is conducted by practicing physicians upon their patients. In a setting where physicians routinely see patients within the context of clinical care, there appears to be a conflict of interest on the part of the physician when they conduct research. In my view, the temptation to employ what the FDA calls "undue influence" upon the patient is too great within the setting of clinical care to conduct research.

In the setting of clinical care physicians can exploit their relationship with their patients. At the minimum they have the opportunity to be an undue influence upon them in other cases they may have the ability to coerce them into participating in research the patients would normally not consider. The FDA allows this type of clinical research to be conducted. In opposition to current FDA and world regulatory policy, I think that this type of research activity ought to be suspended. I think that the goals of research and the goals of patient care are often, if not always, in conflict. Doing what is best for the patient is often not compatible with asking them to enroll in an RCT. In the vast majority of cases the patient will receive no direct benefit from his participation in the trial. In fact it may subject them to additional risk.

A further consideration is the fact that most physicians who engage in clinical research in the context of their private offices have a financial stake in the results. They are often paid by the pharmaceutical companies to recruit test subjects from

their pool of patients and to conduct research upon them. Beyond this they often have a quota of test subjects that they must enroll in a particular study, within a given period of time. This may lead them to urge patients to enroll in research that may not be in their best interest.

Consider a recent case of a physician conducting clinical research within his clinical practice, Dr. Jacobson. He recruits patients and runs clinical trials from his private practice. The majority of his patients come to him for clinical care. He is a neurologist that specializes in Parkinson's disease. Because he runs several concurrent trials, with various medications, at once he is in constant need of new test subjects.

There are rigid deadlines for recruiting and enrolling experimental subjects yet, because his office is rather disorganized, those deadlines often sneak up on him. In other words, he often has to enroll patients in a rush. On a given day Dr. Jacobson, might need 5 patients to enroll in a Parkinson research study with a placebo control (a PCT) by the end of the day. If he is only seeing 7 patients today, he may "insist" or "urge" 5 patients to enroll in the new research study, even if it is not in their best interest. In principle, the patients are supposed to give their informed consent to participate in a PCT, yet in practice, this may not happen.

Some doctors, especially, Dr. Jacobson, may pressure or bagger their patients into signing an informed consent agreement. Doctors like Dr. Jacobson may lie or bend the truth to get a patient to consent. He may suggest to the patient that there is some benefit to his participation, when, in fact, there is not. This practice



of conducting research within clinical care, especially as it is conducted in Dr. Jacobson's office, (even if there did not exist any deception) appears to violate the physician's therapeutic obligation. I think it is unethical, and should be abolished.

The doctor, in a position of authority and knowledge may be able to persuade patients to consent to research that does not benefit them. This practice seems to violate the patient's rights and, at the very least, it certainly hinders this ability to give informed consent. In my view, Dr. Jacobson's actions are unethical- unfortunately this seems to be the norm when physicians conduct randomized trials within the context of the clinical care setting.

Within the clinical setting physicians ought to act in the best interest of their patient. If the results of that treatment can be used to further human knowledge of their medical condition then all the better. Nevertheless the physician must place the patient's individual welfare above that of the common good of society or of answering important scientific questions. Furthering scientific knowledge must be secondary to patient care in the setting of clinical care. Once again, respect for the rights of persons and their right of self determination entails informing them of their options for care and respecting their decisions. I will reiterate that research conducted within the context of clinical care seems replete with ethically suspect practices. These practices lead to a conflict of interest between the patient's care and the physician's goal of conducting research. Patient care, (in the physician's office) should always trump scientific research.

Franklin Miller and Howard Brody have written extensively on this issue. They argue the following:

Given the distinction between clinical trials and medical therapy, as a rule it is undesirable or ethically hazardous for physician-investigators to enroll in their studies individuals with whom they have an ongoing doctor-patient relationship, either for primary or specialty care. Physicians may properly perform the dual roles of treating physician and investigator; the ethical problem arises when these dual roles are undertaken simultaneously with the same patients. Conflicts between patient welfare and scientific investigation, inherent in research are compounded and the potential for exploitation is increased when the investigators have an ongoing physician-patient relationship with research participants.<sup>113</sup>

In this instance, physicians can exploit the trust that is inherent between them and their patients to perhaps convince them to participate in research that they otherwise would not do. The patient may consent to research because he believes that the physician is recommending something that is in his best interest. The patient must be made fully aware of the possible risk and benefits in order to provide informed consent. Some patients believe they will directly benefit from clinical research when they may not. In most instances they will not benefit. When a patient enrolls in clinical trials believing that he will directly benefit from the trial, (when he may not), he is acting under what is known as the therapeutic misconception. When patient care and clinical research are mixed in one setting it is easy to see how patients might mistakenly believe that they are going to benefit from clinical research. After all, why would their caring doctor, who they came to for help, ask them to enroll in a clinical trial, if it was not in their best interest? The issue of the therapeutic misconception will be analyzed below.

The notion of therapeutic obligation has significant ramifications for physicians who routinely enroll their patients in clinical trials. Certain types of trials that employ an inferior treatment or in the case of the placebo no treatment,

appear to violate this principle. Assuming the principle holds, at least within the context of clinical practice, then prima facie, a physician's therapeutic obligation seems to be at odds with enrolling his patients in such trials.

In most cases the patients enrolled in a clinical trial will not benefit directly from participating in the research. In the case where the trial involves the prospect of no direct benefit for the patient's condition then the physician should inform the patient of this. Further, in order to fulfill his obligations he should also recommend against enrolling in the trial if he believes it will not benefit the patient. Yet, in my view, the final decision should belong to the patient. The physician ought to respect the patient's right of self determination to consent to participate in research even if the doctor does not believe is in the patient's best interest.

One might question, whether the doctor should even mention the trial to the patient. If the patient does not know of the trial then there will be no chance of them enrolling in the study and thereby of potentially receiving an inferior treatment. As previously stated, I feel this would violate a person's right to choose and make decisions regarding his person. It is a violation of the right of self determination and the individual autonomy of the experimental subject to withhold this information. The patient has the right to be informed about the trial, (assuming, of course, that the physician is aware of it). If patients with particular conditions were never informed of clinical trials then no one would ever volunteer for clinical research. If no one ever volunteered to participate in clinical research, then it would be very difficult, if not impossible, to make any progress in treating

or curing diseases. I would not go so far as to argue that patients have an obligation to participate, but their participation could certainly be considered an act of altruism. If they are not informed of the trial then they are denied the possibility of engaging in such an act, because their doctor is acting paternalistically.

Although I have been highly critical of the current system which allows physicians to conduct clinical research side by side with clinical care, it should be noted that, in theory at least, it would seem that informed consent is more than simply securing the patient's signature on a document. If the potential test subject is "informed" and not pressured into agreeing to the research, then his rights have not been violated. In practice this may be difficult to guarantee given how subjects are recruited and how informed consent is actually obtained.

It is possible that some doctors might exploit their relationship with patients in order to get them to participate in a clinical trial. Some patients may fear repercussions if they do not consent to participate in the clinical trials that their doctors recommend. They may feel that by not acquiescing to the request that their relationship with the physician and their future medical treatment and wellbeing will be affected. Whether this is a legitimate concern, I am not sure. If a doctor was pressuring me into participating in a clinical trial, I would simply find a new doctor. I am not sure why more people do not adopt this approach.

Although some patients might have the option of going elsewhere, others are required by their insurance to visit specific physicians. This restriction impairs their ability to leave and seek treatment elsewhere. As it stands, the power of the

physician to coerce or unduly influence patients into consenting to clinical trials is a legitimate ethical concern. Given the possibility of coercion, research of this type- conducted in the context of clinical care ought to be severely restricted.

There is a clear conflict of interest in many cases when a physician conducts clinical research within his private practice. In many cases physicians are paid signing bonus that can total thousands of dollars per patient for each one recruited to a clinical trial. In the case of trials conducted at university or teaching hospitals or practices, there are just as many incentives for physicians to recruit patients. There are just as many opportunities for the goals of patient care and clinical research to come into conflict. They can include the need to produce clinical results and new treatments to justify academic advancement and tenure, the need to secure funding sources which often time entail grants to test the efficacy of new treatments, and the need to produce revenue for the institution. The reasons sketched above clearly illustrate the inherent conflict of interest that normally exists when clinical research is conducted within the context of clinical care.

In my view more phase 2 and phase 3 clinical trials sites ought to be created for the express purpose of testing the efficacy of new medical interventions. There does not seem to be a reason why a physical could not recommend that patients consider trials conducted at different sites by different researchers. If clinical trials were conducted in this way, then the chances of patients being coerced by their personal physician would be much reduced. As I argued earlier, I think that if the informed consent process is conducted properly, then there should be a rather limited possibility for either coercion or exploitation. If the patient is

mislead or misinformed then the condition of informed consent is not met.

Without informed consent the participation of the patient is unethical.

Nevertheless, whether patients were recruited from clinical practice or not, once they have given their informed consent, they are no longer a patient but now experimental subjects. From the perspective of the physician-researcher they are test subjects once they consent to participate in the research trial; at least within the scope and limits of the intervention under consideration within the trial. This does not mitigate the obligations that the physician has to the patient regarding other medical issues or concerns unrelated to the trial. For example, if my physician request that I enroll in a clinical trial testing a new allergy medication, then it does not follow that he does not have an obligation to treat an unrelated medical condition, such as psoriasis.

In such an instance, as test subjects, they should not have an expectation of therapeutic benefit. Beyond this, informed consent agreements are written in lay terms so that the average person can understand what they are consenting to. Most consent agreements clearly state that patients may freely enroll and freely withdraw at any time from a study without any repercussions. If potential test subjects have taken the time to read, question, and understand the informed consent agreement then they should not be acting from what is termed the therapeutic misconception. The therapeutic misconception occurs when patients believes that they will benefit from the clinical research, when, in fact, they will not. If they are not pressured or hurried and if the informed consent process is conducted appropriately and ethically, then they should understand the risk and

benefit involved in the trial. Given the nature of many informed consent agreements, it is unreasonable for any rational being to expect to attain any therapeutic benefit from their participation in a clinical trial if there is none to be had.

As research subjects their “rational expectations” should be different than the “rational expectations” of patients. Given that they have no reason to expect a therapeutic benefit, (as long as this is explicitly stated in the informed consent form), then it seems unreasonable to burden the clinical researcher with the notion of therapeutic obligation. Once again if informed consent is properly obtained, then the experimental subject should not be acting under the therapeutic misconception- this is true, in principle, even if they were recruited by a physician/ researcher.

### **Therapeutic Obligation and Clinical Equipoise**

I defend, as ethically permissible, a specific type of Randomized Control Trials: Randomized Control Trials with a placebo control (PCTs). This defense stands in the face of harsh criticism by several critics<sup>114</sup>. In fact this defense is at odds with policy statements such as that of the Tri-Council of Canada. PCTs in particular have been attacked ethically on a number of grounds. Nevertheless it is my belief that both RCTs and PCTs are normally ethically permissible just as long as certain conditions are met.

There are several arguments against both RCTs and PCTs. One of the principle arguments against them is that enrolling patients in such trials violates the physician’s duty to provide the patient with an optimal treatment. In the

previous chapter I argued that so long as patients are informed about the potential risk and benefit of enrolling in clinical research then the decision to enroll ultimately rest in their hands. The doctor should not act in a paternalistic manner on their behalf. When the doctor does this, they are also violating their rights. By the same token the doctor should not enroll them in research without their consent or knowledge, nor should the doctor refrain from offering them the opportunity to participate in clinical research.

Sven Hansson argues that “It is a violation of competent medical practice to offer a patient a treatment known to be inferior, even if the patient consents.”<sup>115</sup> I agree that in clinical practice, a physician ought not to employ a treatment that he considers to be inferior, but clinical research is not the same as clinical practice. This line of defense has been employed by Franklin Miller and Howard Brody.<sup>116</sup> They mark a distinction between clinical research and clinical practice. They claim that a clinical researcher is not bound by the same moral obligations as a physician. Although I sketched a version of this argument earlier, I will reconsider the viability of this defense now.

It has been argued that a physician, based in part upon the principle of beneficence, has an obligation to provide each patient with the optimal care. This is sometimes termed ‘therapeutic obligation’. In general, I agree with this assessment; doctors have an ethical obligation to provide their patients with the optimal care. When patients visit a doctor they have a rational expectation that they will provide them with the best care possible. Doctors that ignore this



obligation are ignoring a fundamental duty of healthcare providers; as such they are acting unethically. Does this same obligation apply to clinical researchers?

In my view the therapeutic obligation is mitigated when patients freely chooses to enroll in a clinical trial. As long patients are informed and consents, then the physician is free to enroll them in the clinical trial. It is reasonable to maintain, as Miller and Brody do, that the concept of therapeutic obligation does not apply within the context of clinical research. This does not absolve a clinical researcher from particular duties and obligations to test subjects, but in my view, those obligations are different. Miller and Brody have argued that the notions of beneficence and therapeutic obligation do not apply to clinical researchers or physicians in the clinical care setting when conducting clinical research. They maintain that the expectations of research subjects are significantly different than those of a patient. They present these arguments in the context of equipoise.

The notion of equipoise has been examined extensively by Benjamin Freedman. This same concept is termed the “uncertainty principle” in many European journals.<sup>117</sup> According to Freedman, “The ethics of clinical research requires equipoise--a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial”<sup>118</sup>. In a later article Freedman states the principle as follows:

As a normative matter, it defines ethical trial design as prohibiting any compromise of a patient’s right to medical treatment by enrolling in a study. The same concern is often stated scientifically when we assert that a study must start with an honest null hypothesis, genuine medical uncertainty concerning the relative merits of the various treatment arms included in the trial’s design. These principles allow for testing new agents when

sufficient information has accumulated to create a state of clinical equipoise vis-à-vis established methods of treatment.<sup>119</sup>

Freedman and others argue that a state of equipoise is necessary in order for clinical trials to be ethically permissible. Even if I were to accept this requirement, which I do not, it is important to note, that not everyone agrees as to what constitutes a state of equipoise. Some argue that a state of equipoise obtains if the doctor recommending enrollment in the experiment does not know which treatment is better. Others say that the doctor's knowledge is not the important thing; rather it is what the scientific community knows, or believes. Others also claim that even if the treating physician does not know which treat is superior, there is still no equipoise unless the doctor has no reason whatsoever to prefer one treatment. Generally this would be a difficult condition to meet as physicians usually have some reason to prefer one treatment over another- in which case the state of equipoise does not obtain.

Those that accept the definition of equipoise defended by Freedman, Emanuel and others argue that it is unethical to engage in a comparative study involving what is known to be an inferior treatment by the medical community. In cases where the scientific community does not know which treatment is better physicians are not violating their therapeutic obligation to their patients by asking them to enroll in clinical trials. Even if we accept this definition, and maintain that it is unethical to run a study unless there is genuine uncertainty, it still does not follow that all trials will be unethical even if they involve treatments which the scientific community as a whole maintain are ineffective.

Consider the following case: Treatment X is held as an effective standard treatment for ailment A. Treatment Y is a new, untested, treatment for ailment B. The drug company that developed treatment Y would like to run a RCT (either an ACT or PCT) to confirm the efficacy of the new treatment. As the notion of equipoise is explained above, it is, *prima facie*, unethical to conduct the trial. It is claimed by opponents of RCTs to be unethical because all patients with ailment A have a right to (the best) treatment for their condition. I argue, *contra* Freedman and others, that a state of equipoise is not a necessary requirement. I maintain that it is reasonable to offer the choice of enrolling in a clinical trial to any patient. I further maintain that it will be reasonable for patients to enroll in the trial if the standard therapy is ineffective in treating their condition, but that they are free to enroll even if the standard treatment is effective.

At times Freedman makes it seem as though equipoise is a difficult condition to meet, at others he sounds as if the requisite uncertainty is common place, "... considering the uncertainties of medical science and the heterogeneity of patient populations, it is rare for the medical community to be in accord as to which treatment is the best."<sup>120</sup> He seems to admit that there is seldom a consensus about which therapies are "the best" for a given medical condition. If this is the case, then the ethical requirement of equipoise is easily satisfied. It is certainly debatable as to whether or not a treatment is the universally recognized standard of care.

I side step most of this discussion by denying that a state of equipoise is necessary for the ethical permissibility of a clinical trial. As I have argued earlier,

the patient's right of self determination trumps the physician's therapeutic obligation. Against Freedman's view, I claim that rights of patients, specifically their right of self determination, and ability to give informed consent can resolve most of these issues. I have also argued that even if there is an accepted standard treatment, if that treatment is ineffective for the patient, then the therapeutic obligation would not preclude the physician from asking a patient to enroll in a PCT. Furthermore, even if the standard treatment worked, patients still have a right to enroll in clinical trials, thereby circumventing Freedman's arguments regarding the physician's therapeutic obligation.

I argue that both RCTs and PCTs are generally ethical because test subjects have the right to participate in such trials as they deem fit. Beyond this clinical researchers are not violating their therapeutic obligation because, in my estimation, they don't have one. The idea that informed consent can answer many ethical objections to clinical trials is also defended by Robert Temple.

Temple is one of the key figures in the design of the FDA's drug review policy. Temple argues that, "IRB's (Institutional Review Board) and patient consent forms, which tell patients exactly what they may be getting into, can assure the ethical nature of drug trials."<sup>121</sup> This view has been attacked by Freedman and others. Freedman calls this the "Myth that informed consent to placebo-control makes them ethically acceptable."<sup>122</sup> He claims that "This powerful appeal to the claims of liberty fails on theoretical and practical grounds. As a theoretical matter, every major code of ethics for human experimentation, from the Nuremberg Code to the present has recognized that adequate subject

consent and an acceptable risk/benefit ratio are two independent preconditions for clinical research.”<sup>123</sup>

Freedman and those that defend his position are wrong. They claim that there are several requirements for ethically permissible clinical research. They deny that person's are at liberty to consent to dangerous clinical research. I disagree with this misplaced paternalism. Furthermore simply citing a moral code does not show that the right of self determination is not a necessary component of ethically permissible clinical research. In my estimation, an acceptable risk/benefit ratio is not a necessary condition for the ethical permissibility of clinical trials. A potential experimental subject ought to be the ultimate judge as to what counts as unacceptable risk. If the risk is too great, then they will not enroll in the clinical trial. Although Freedman may believe otherwise, most people that enroll in clinical research are competent to make such a decision. Again Freedman thinks that citing a moral code demonstrates that his point is cogent- it does not. By the same token, I must admit, that citing the current FDA policy does not settle the issue either. Yet, to be clear, my position is significantly different from that of either Freedman or the FDA. The FDA, for example, allows informed consent to be waived for a variety of reasons- I challenge the ethical permissibility of such a waiver in most circumstances.

Once again, I would argue that the rights of persons, specifically their right of self determination and their liberty and autonomy over their person is sufficient (along with informed consent) for one to ethically participate in a scientifically valid trial, regardless of the risk. Whether or not reasonable persons would, in

fact, agree to participate in such a trial is another matter. Perhaps they would not consent to the trial, but in the end it is their choice. To sketch a brief example: if my child was suffering from a debilitating illness, then I would be willing to consent to almost any type of clinical trial, regardless of the risk, if it held the possibility of gaining knowledge and insight into a cure for their condition. Some argue that this is somehow a coercive circumstance- I deny that it is. Coercion involves a threat of force or harm, none exist in this instance. Other ethicists, would allow doctors to experiment willy nilly upon you, without your permission, so long as time is short and the doctor must make snap decisions. Which case is more ethically troublesome? The judgment of risk and the decision to enroll in a clinical trial is not a decision for the IRB or for the physician; rather it is the patient's decision. Furthermore, not obtaining informed consent is much more problematic than asking someone their permission to participate in a clinical trial. No one else ought to make the decision for the patient. It is a paternalistic violation of a patient's rights to presume to make the decision for them.

The current FDA guidelines are paternalistic and violate the rights of competent persons. The current guidelines require that an Institutional Review Board (IRB) assign each study to a particular category of risk and benefit category. Even so it does not preclude the IRB from approving a study with a high risk. Nor does the policy explicitly state that subjects are prohibited from enrolling in a study, even if their enrollment entails that they will be subjected to tremendous risk. The risk involved in the trial will be stated in the informed consent agreement. In my view, any competent patient should be aware of the

benefit or risk involved in the clinical trial. I will consider the FDA requirements and IRB system in more detail in the final chapter.

In another paper on this issue Deborah and Samuel Hellman argue the following:

One might suggest that the patient has abrogated the rights implicit in a doctor-patient relationship by signing an informed consent agreement. We argue that such rights cannot be waived or abrogated. They are inalienable. The right to be treated as an individual deserving the physician's best judgment and care, rather than to be used as a means to determine the best treatment for others, is inherent in every person.<sup>124</sup>

This is a rather tenuous position to maintain. It is difficult to argue for rights in general, let alone to establish that a right is inalienable. There are several questions that can be raised by this idea. 1) Does a patient really have an "inalienable right" to the best care and judgment? 2) If we disagree about what constitutes the "best treatment, is the physician then going to force a treatment upon the patient? 3) Does this violate the individual patient's right of self determination?

Let us consider each of these questions in turn. In my view, in general, a patient has a right to optimal care. Yet, I would not argue that this right is absolute. *Prima facie* the patient enjoys this right, but it is not absolute. I may have a right to a liver transplant, but that does not mean that I will receive one. Given the scarcity of resources the corresponding obligations entailed by this right may go unfulfilled. The fact that I may freely choose to waive this right, seems to indicate that it is not inalienable. The patient ought to have the final say regarding what will be done to his person.

This “right” to optimal care can be waived by the patient. This right is not absolute nor is it inalienable as the Hellmans' maintain. We need not ask the patient's motivations for choosing to participate in clinical research- even if this entails he may not receive optimal care. It might be money, it might be altruism. In the end, we are not in a position to ascertain the patient's motives, and in this context, it is irrelevant just so long as he was not coerced by the physician/researcher. The physician has an obligation to inform the patient of the risk and benefit inherent in the research. Further, the physician should not exploit his relationship with the patient in order to persuade him to consent to participate in research. (Which given the current reality of how research subjects are recruited from doctor's offices for phase 2, 3 and 4 clinical trials raises many more ethical concerns.)

Again, let us consider what it means to have an inalienable right. If a right is inalienable, then there are no circumstances whatsoever upon which it could be given up. If we were to assume that this right to optimal care is “inalienable”, then it would seem that a patient that seeks treatment for a condition must accept such optimal treatment as the physician deems fit.

It would seem, in the view of the Hellmans, that when there is a disagreement between the patient and the physician, that the views of the physician take precedent. If the physician thinks that a given medical intervention is in our best interest, then we must accept it. The physician's obligation to provide optimal care trumps the patient's right over his person and his right of self determination. In other words, patients will be forced by physicians to take their medicine, the



same way small children are forced to eat their vegetables by their parents. Like a mother that scolds her child into swallowing his medicine, so too, a physician must force patients to receive any care he feels will be the “optimal”. All of this follows from the idea that patients cannot waive their right to optimal care. This type of paternalism is a clear violation of the patient’s right of self determination. Further it would have serious implications for all type of clinical research- from observational studies to PCTs.

Benjamin Freedman concludes his paternalistic arguments against patient rights by claiming that most subjects don’t understand what they are consenting to. He claims that most of them are uninformed about what is involved in clinical research. He says that from a practical perspective, most subjects that consent to clinical research may not be “informed”. Freedman argues that, in practice, most patients do not understand the research that they are consenting to participate in. He claims that they don’t grasp what is entailed by randomization, blinding or placebo control. According to Freedman, most experimental subjects consent to participate in research because they believe it will help to alleviate their condition. This is known as the therapeutic misconception. In his view almost all test subjects that enroll in clinical trials do so because they are acting under the therapeutic misconception. If this were true, then, because the condition of informed consent is not satisfied (a condition that there is near unanimous consensus is necessary in most cases for a clinical trial to be ethical) then virtually no clinical trials would be ethical!

### **Therapeutic Misconception**

We have discussed the notion of the therapeutic misconception in passing, but, at this juncture, I feel that it is appropriate to consider it in detail. One definition of the therapeutic misconception is stated by Paul Appelbaum as follows: A therapeutic misconception occurs when a subject transfers to the research setting the presumption that obtains in ordinary clinical treatment: that the physician will always act only with the patient's best interest in mind.<sup>125</sup> The therapeutic misconception occurs when the test subject believes that his participation in clinical research will directly benefit him when, in fact, it may not.

In most cases, there is no guarantee of direct benefit. Yet, by the same token it might have beneficial effects upon the test subject's condition. Most opponents of clinical trials assume that there is no direct benefit to the experimental subject, but the reality is that there may be a prospect of direct benefit. For some patients, clinical trials offer a unique opportunity for treatment. In order for test subjects to give their informed consent, they must be made aware of the fact that they may not (will not in some cases) directly benefit from the research study. In the case of PCTs, one group of patients will receive a placebo. In this instance, the placebo control group will not benefit directly by their participation in the study. The other group which receives the experimental intervention may benefit- if the drug is effective, but again this is not guaranteed.

It has been empirically demonstrated (by exit surveys conducted on experimental subjects) that many patients that enroll in clinical research are under the mistaken impression that by enrolling in a clinical trial, they will directly

benefit from the treatment. In some cases this is possible, but in others it is not. For the sake of argument, let us assume that Freedman is correct and virtually no patient ever fully understands what they are consenting to, would this preclude all clinical research? It would seem that on his views most patients don't understand clinical research well enough to give their informed consent. It then follows that almost all clinical research is unethical because it is unethical to conduct experiments upon individuals who do not understand what they are consenting to. It then follows then on Freedman's view that we are left with the absurd conclusion that no clinical research is ethically permissible because no test subject can provide informed consent!

I admit that if a person consents to research as a result of a therapeutic misconception, then the research may be unethical, but it does not follow that it always is. If it is unethical it is because the experimental subjects have not given their "informed" consent. In such a circumstance they did not truly understand the nature or their role in the clinical trial and because of this could not give their informed consent. In order to respect the right of self determination of potential test subjects, they must be informed and understand how their participation in the research may affect them. I do not believe that people are so ignorant that it is not possible to obtain informed consent. It seems unlikely that every test subject is enrolling in RCTs or PCTs does so as a result of the therapeutic misconception. If the informed consent process is conducted properly, then the patient should not be suffering from the therapeutic misconception.

In my view, therapeutic obligation does not preclude requesting that a patient enroll in a clinical trial. As noted earlier however, it can lead to a possible conflict of interest. The personal goal of the physician to test a new therapeutic intervention may be at odds with providing optimal care to the patient. One possible solution to this potential conflict of interest is to recommend patients volunteer for research studies in which the physician has no role or stake. By the same token, arguing that a patient should not even be told of the clinical trial is a stance based on an outdated paternalistic notion of the relationship between the physician and the patient. The patient ought to be given the opportunity to enroll in research. Hopefully such research will benefit the patient in the long run.

#### **Alternative Concepts of the Necessary Requirements of Ethical Research**

What are the essential conditions for ethically permissible research? In a paper titled, “What Makes Clinical Research Ethical?” published in the *Journal of the American Medical Association*, Ezekiel Emanuel, David Wendler and Christine Grady (all of the NIH) argue for “7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies.”<sup>126</sup>

Although Emanuel et al. argue that there are seven necessary requirements, they point out that if asked most researchers will argue that informed consent is the only essential requirement of ethical research. “Informed consent is the answer most US researchers, bioethicist, and institutional review boards would probably offer.”<sup>127</sup> In their view informed consent by itself is not sufficient for ethical clinical research.

Ezekiel Emanuel et al. delineate the following criteria as being necessary for ethical clinical research:

(1) value- enhancements of health of knowledge must be derived from the research; (2) scientific validity- the research must be methodologically rigorous; (3) fair subject selection- scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio- within the context of standard clinical practice and the research protocol, risk must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risk; (5) independent review- unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent- individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects- subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical.<sup>128</sup>

In my view all of these are important considerations, yet I am less certain that they are all necessary or that collectively they are sufficient to guarantee the ethical permissibility of research. I will consider their arguments for each requirement in turn.

### **Value**

Does the research have value? Does it fill an epistemic need? If the answer is no, then it should not be done. In most cases, the answer is not quite so clear.

Emanuel et al. argue that the research must have the potential to answer important scientific questions and be worthy of spending the limited resources that society has to spend on medical research. Further it must be valuable enough to justify risking potential harm to human beings. “Examples of research that would not be socially or scientifically valuable include clinical research with nongeneralizable

results, a trifling hypothesis, or substantial or total overlap with proven results.”

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In part it appears that their examples conflate scientific validity with value in general. A better statement of what they have in mind might be that research must have the potential to lead to improvements that can lead to the betterment of mankind or to those individuals afflicted with a particular condition. In principle this might appear very straight forward, but in practice it is not. How are we to weigh the cost and benefits derived from one research study with another? In principle we can talk about the betterment of mankind, yet in practice many of these studies are funded by large pharmaceutical companies. No doubt they think value is of paramount importance, but what they value may not be the betterment of mankind but rather profit.

Such a view might sound cynical, but the empirical evidence bears it out. Millions of people are dying from diseases that do not have an effective treatment while pharmaceutical companies are developing treatments for toe nail fungus. Value is an important component of research, but if Emanuel et al. are correct, then most clinical research fails to meet this condition. This is the case because most of the research conducted does not have any significant value. It will not promote a social good or cure a raging epidemic. Beyond that, it is not even a step in that direction. If this is the case then most clinical research is unethical, as it fails to meet his first condition.

I doubt that Emanuel and his colleagues would want to make such a strong claim, but it is consistent with their views. “Beyond not wasting resources, researchers should not expose human beings to potential harm without some

possible social or scientific benefit.”<sup>130</sup> Again because of the nature and limits of the patent process in the United States, pharmaceutical companies must constantly develop new treatments, even if the standard treatments are effective. This leads to a possible scenario where the value of the research is negligible from a scientific standpoint, but of great value from an economic perspective. Is it ethically permissible to risk harm to experimental subjects so that pharmaceutical giants can increase their profits?

Emanuel seems to restrict his analysis to publically funded research. If all clinical research were funded by public dollars then I would agree that one ought to focus on projects that will serve the common good of society. In essence this is compatible with a utilitarian calculation- maximizing social utility. Unfortunately the vast majority of clinical research is not funded with public money. Most research is funded by private research dollars. This money is often spent on developing medical interventions that are not aimed at the betterment of mankind, but towards the goal of filling the coffers of private businesses. If we extend his schema to all clinical research, then we may be forced to admit that most clinical research violates this principle.

I think that this problem can be resolved. The dispute as to what has value depends in part upon who is asked. The scientist, pharmaceutical company and research subject may all have different opinions on this matter. To deny this seems unreasonable. All have competing and sometimes conflicting goals, so it would seem to follow that they may not agree as to the value of a particular clinical trial. In the end, the opinion that matters, in my estimation, the most is

the individual research subject. They are the one that stand the most to lose by participating in a clinical trial. If he is willing to risk his life and limb for the research, then, in his opinion it must have value. If it did not, then it would not be reasonable for him to participate. In order to avoid a number of ethical dilemmas that might result by questioning the value of the research, we ought to leave this discussion in the hand of those who have the most to gain or lose from the research- the patient/ test subject.

What has value? This will depend, in part on the individual. For example, if my child were afflicted with an illness, I would gladly consent to participate in all sort of clinical trials that were aimed at developing a cure. I might suffer severe side effects or even die, but it would all be worth it if my participation contributed in some small measure to an eventual cure. On the other hand, if my child was not sick, I probably would not consent to participate in the research. To a father, that is desperate to find a cure for his child, participating in a clinical trial that holds the possibility of a cure for his child is of significant value. That father may find it well worth the risk to his life. On the other hand, to the father with a healthy child it is not worth the risk because he has nothing of value at stake in the trial.

Value is an often lurking variable in the ethical discussion of the ethical permissibility of clinical research. It is often assumed that reasonable people will agree about what has value, but this is seldom the case. It is often taken for granted that the research has value, but again, what value does it have and to whom? I feel that the question of value ought to be determined by the research



participant. If he considers the research to be valuable, or stands to gain something of value from participating in the trial, then it is ethically permissible for them to participate in the research.

### **Scientific Value**

I argued earlier that broadly speaking the most important ethical criteria for clinical research were informed consent and respect for right of self determination. However I also defended the thesis that research must employ a scientifically valid methodology. Emanuel et al. concur with this assessment. “For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan.”<sup>131</sup> It seems clear that risking harm to test subjects when the methodologies employed cannot resolve the question under consideration is unethical. If the experiment lacks validity, then as Emanuel et al. say, “Without validity the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.”<sup>132</sup>

In the previous section I argued that the test subject ought to decide what has value, in this particular case, I think the experts- the physicians, statisticians, and philosophers ought to determine whether or not a particular research methodology is valid. I would hope that they can provide a justification for their analysis for those that are not experts, and for the sake of argument, let us assume that they can.

I will note that this issue is not as straight forward as it may seem. If we reconsider the ECMO case from the previous chapter, both statisticians and physicians disagree about how to interpret the data and what counts as evidence and confirmation. In this case, those intellectual controversies of Bayesian or Pearson- Neman interpretation of the data cost several newborns their lives! As such, this issue of the importance of scientific validity cannot be over looked.

### **Fair Subject Selection**

The notion of “fair subject selection” is often argued for within most codes of research ethics. Emanuel et al. claim that this is a necessary condition of ethical clinical research. Subject selection involves determining who is eligible to participate in clinical research. The authors argue that the risk and benefit of clinical research ought to be shouldered by everyone. It should not be determined by “vulnerability, privilege, or other factors unrelated to the research...” In theory most research is open to everyone within a community, except those who may require special protections such as children, the elderly or women that are or who may become pregnant.

Once again, adherence to these principles seems to break down in practice. Many research studies have been moved overseas, in part, because it is easier to recruit test subjects. Is it ethical to recruit people to participate in experiments for which they have little chance of receiving direct benefit? As the authors argue, “In the past, groups sometimes were enrolled, especially for research that entailed risks or offered no potential benefits, because they were "convenient" or compromised in their ability to protect themselves, even though people from less

vulnerable groups could have met the scientific requirements of the study.”<sup>133</sup>

Unfortunately, these practices were not left in the past. Such practices are ongoing both here and abroad.

Although Emanuel et al. cite this as a necessary condition for the ethical permissibility of clinical research, they seem to back off of this claim when they say, “This does not mean that individual subjects and members of groups from which they are selected must directly benefit from each clinical research project or that people who are marginalized, stigmatized, powerless, or poor should never be included.”<sup>134</sup> With the requirement watered down to such a degree it seems empty of any normative force. If it is ethically permissible to employ people that are “marginalized, stigmatized, powerless, or poor” then why bother having “fair subject selection” as a necessary requirement of ethically permissible clinical trials. Perhaps they recognize the implications of such a requirement and back away from it. As has already been discussed in a previous chapter, the poor are systematically employed in phase 1 clinical trials. If it is unethical to employ them, then it follows that most phase 1 clinical trials (regardless of methodology) are unethical.

In practice the burden of clinical research is often shouldered by those who have the least to benefit from it. In the end, if those individuals choose to participate, and have given their informed consent, I maintain that their participation in clinical research is ethical permissible. Whether they were able to actually give informed consent is a contentious point, as discussed above. To conclude the discussion of fair subject selection, meeting this condition may be as

simple as offering the research to anyone who is willing to participate, or on the other hand, as it may be as complicated as banning most research conducted in developing countries.

### **Favorable Risk- Benefit Ratio**

The idea of a favorable risk- benefit ratio is another way of saying that the value of the research must outweigh the risk. In a narrow sense the value in question is restricted to the subject. The benefit to the individual subject must outweigh the risk, but as noted above, this is seldom the case.

Very few research participants will benefit directly from their participation in research. In most cases, the researchers cannot be certain that the medical intervention under consideration will not do more harm than good to a particular individual. The rationale for clinical research is to test the efficacy of an intervention. If you are testing the efficacy, then ipso facto you don't know if it works. If the physician does not know that an intervention works, then he cannot guarantee any direct benefit to the individual participating in the study. Even if the physician was certain that it worked he cannot guarantee that the subject will receive it. The subject may be randomized into an arm of the study that receives the placebo or another form of treatment.

In view of Emanuel et al. "Clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the

risks.”<sup>135</sup> As these conditions are stated, they seem to collapse into their first two conditions, that the research be scientifically valid and that it have value for society.

In the end, I maintain that the individual subject must decide if participating in the research is valuable to them. If he deems it of value, then it is. If he decides it is not worth the risk, then it is not. Freedom of choice and respect for right of self determination is what matters most in these considerations. Otherwise, if we interpret these requirements in a strong sense, very few clinical studies would meet this “necessary” requirement. If this were the case, then most clinical research would be unethical.

### **Independent Review**

Independent review of a research protocol is an important consideration for the ethical permissibility of clinical research. As Emanuel et al. note:

Investigators inherently have multiple, legitimate interests—interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct, and analysis of research.<sup>136</sup>

Researchers are sometimes blinded by their desire to find the truth. In that quest for knowledge they may, intentionally or inadvertently, place their interest in research above the interest of the persons being employed in the research.

It is the view of Emanuel et al. that independent review is a necessary requirement of ethically permissible research. In short, I disagree. I think that research can be conducted in an ethical manner, without violating the rights of the

individual, without having an independent agency review it. In practice most ethical and legal regulations require review of clinical research proposals for both epistemic and ethical considerations. Part of the reason I object to independent review and feel that it is not a necessary requirement, is because it would involve a “paternalistic” role of the “independent review board” towards the subject. The IRB is making the determination of risk for the subject. The assessment of risk and the overall value of the research ought to be determined by the research participant. Ultimately, in principle, I do not believe that independent review is a necessary ethical requirement. In practice independent review may serve an important role to ensure that scientifically valid research methodologies are employed and that the questions being addressed by the research are non-trivial.

### **Informed Consent**

I find it interesting that what I would consider to be the most important requirement for the ethical permissibility of clinical research ranks 6<sup>th</sup> on the list Emanuel et al. develop of necessary requirements. As they say, “To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate.”<sup>137</sup>

As was noted in the preceding chapter, Benjamin Freedman argues that most adults participating in clinical research within the US do not meet the condition of being “informed”. If this criticism holds true for participants from the US, (where we have a general science education) what about those individuals recruited from

developing countries where they lack most basic science education. Can the “marginalized, stigmatized, powerless, or poor” give informed consent to research? Can they ever reach the level of being “adequately” informed? Subjects recruited from such settings may not have a clear comprehension of the most basic medical principles. How is one to explain a virus, or a vaccine to someone that hasn’t the slightest notion of such a thing? Is it possible to obtain informed consent from such a person? If the answer is no, then most research should be banned from the developing world! I will consider this argument in detail in chapter 4. For now, I will grant that informed consent is a necessary requirement of clinical research.

### **Respect for potential and enrolled subjects**

What does respect entail? Emanuel et al. seem to think that, among other things it means following the letter of the law regarding privacy. It also entails allowing subjects to withdraw from research whenever they would like. Respect also requires that if new information pertaining to the intervention is gained during the course of the study that might impact the individual negatively or positively they should be told- or withdrawn from the study. And finally they believe that respect requires the health and wellbeing of test subjects be monitored during the study.

Emanuel and his colleagues have performed an adequate job of delineating the obligations of the clinical research towards their test subjects. I have argued that the obligations of the physician are different from those of the clinical researcher, and I believe that this is a good first step towards a positive statement of those

obligations. I think that each of these criteria ought to be explained in detail, as opposed to being lumped under “respect for test subjects”. But I think that these obligations are founded upon respect for the right of self determination of each competent person.

### **Are These Seven Requirements All Necessary and Together Sufficient?**

Although I have defended the ethical permissibility of clinical research on the basis of respect for right of self determination and the liberty of the test subject to choose to participate in such endeavors, it does not mean that clinical researchers do not have further obligations to test subjects. Researchers have several obligations to the subjects, including several that were made by Emanuel and his colleagues. Those requirements include: 1) Respecting their privacy; 2) Allowing subjects to withdraw from research whenever they would like; 3) Stopping a research study if new information pertaining to the intervention is gained during the course of the study that might impact the individual negatively or positively; 4) And monitoring their health and wellbeing during the study. Emanuel and his coauthors argue that these requirements are necessary and sufficient for clinical research to be ethical. I argue that they are wrong for several reasons. They do not articulate, in a coherent manner, that these requirements are universally required. I attest to this as we consider their words on this matter:

These 7 requirements for ethical clinical research are also universal. They are justified by ethical values that are widely recognized and accepted and in accordance with how reasonable people would want to be treated. Indeed, these requirements are precisely the types of considerations that would be invoked to justify clinical research if it were challenged. Like constitutional provisions and amendments, these ethical requirements are general statements of value that must be elaborated by traditions of



interpretation and that require practical interpretation and specification that will inherently be context and culture dependent.<sup>138</sup>

What does it mean to say that these requirements are “universal” and yet “must be elaborated by traditions of interpretation... that will inherently be context and culture dependent”. The preceding paragraph is incoherent. A requirement cannot be “universal”, and at the same time relative to “context and culture”. It seems to me that because of the way they have stated their view they are open to the criticism that they are invoking some form of ethical relativism based on culture and cultural traditions. If this is the case, their notion that these principles are universal seems untenable.

In the end, they have articulated several considerations that are obligations of clinical researchers. Yet I do not feel that each is a necessary condition, nor are they collectively sufficient to guarantee the ethical permissibility of clinical research. As argued before in each section, they have not demonstrated with sufficient force that each condition is a necessary element of ethically permissible clinical research. At most, the majority of these “requirements” are guidelines that may be taken into consideration, but they are not necessary and/or sufficient for ethical clinical research.

### **Ethical Permissibility of RCTs: Respect for the Right of Self Determination**

In this chapter I have argued that the concepts of right of self determination and informed consent taken together go a long way towards answering the question of the ethical permissibility of clinical trials. It is assumed that the

clinical trials in question are scientifically valid and that they are designed to answer non trivial questions. In defense of both RCTs and PCTs I argued against the necessity of equipoise as a necessary condition for the ethical permissibility of those trials. I have argued that informed consent is obtained properly, then the therapeutic misconception should not obtain. Furthermore I do not believe that people are so ignorant that it is not possible to obtain informed consent. It seems unlikely that every test subject is enrolling in RCTs or PCTs does so as a result of the therapeutic misconception. If the informed consent process is conducted properly, then the patient should not be suffering from the therapeutic misconception.

#### **Chapter 4: The Significance of Moral Codes and Oaths in the Context of Clinical Research**

In this chapter I will consider the moral significance of oaths and codes in reference to the discussion of the ethical permissibility of clinical research. I argue that many contemporary clinical trials violate several principles of both the Nuremberg Code and Declaration of Helsinki (Declaration). A great uproar has ensued over changes to several provisions of the Declaration regarding the ethical permissibility of placebo controls. In fact, the FDA does not endorse the current version of the Declaration. The FDA has reverted to an earlier draft of the Declaration to govern research conducted outside of the United States. I think that the issues regarding the ethical permissibility of the use of a placebo control can be resolved, but there are several other Principles contained in the Declaration that raise significant ethical questions. Several principles appear, *prima facie*, to be systematically violated by research conducted in developing countries upon vulnerable populations.

One way these issues can be resolved is by adopting the minimalist approach to the ethical issues which I defended in the previous chapters. Instead of thirty-two principles as in the Declaration or even the ten in the Nuremberg Code, I have defended two necessary criteria for the ethical permissibility of clinical research. In my view the right of self determination is a *prima facie* right of every competent person. This right provides for the freedom and provides the foundation for an individual's ability to give informed consent to participate in clinical trials. Respect for the right of self determination of each experimental subject is a necessary condition for ethical research. Another necessary condition

for ethically permissible clinical research is that informed consent is obtained from experimental subjects. Taken together the right of self determination and informed consent (in most cases) are necessary and sufficient in normal circumstances for clinical trials to be ethically permissible; provided that the research methodology is scientifically valid and the hypothesis being tested is of scientific merit or value.

Although I have defended the ethical permissibility of Randomized Control Trials on the basis of respect for the right of self determination, individual autonomy, and the liberty of the test subject to choose to participate in such endeavors, there are other means to evaluate the ethical permissibility of clinical research. As noted above, I focus on two main criteria for the ethical permissibility of clinical trials whereas both the Nuremberg Code and Declaration of Helsinki have many more conditions; some of those conditions are compatible with my views, others are not.

### **Moral Codes and Oaths**

In this section the importance of moral codes and oaths will be considered. Specifically I will examine the importance and relevance of the Hippocratic Oath, the Nuremberg Code, and the Declaration of Helsinki. These documents are significant because they endeavor to speak for humanity regarding the universal conception of the person and the obligations of physicians and researchers to their patients. Both the Nuremberg Code and the Declaration of Helsinki attempt to address the myriad of concerns that are raised when one experiments upon human beings.

I have argued that respect for the right of self determination is a crucial element for the ethical permissibility of clinical research. Others have employed respect for autonomy as the basis of ethical conduct for clinical researchers.<sup>139</sup> “This principle forms the basis of the ethical obligations in research... Individuals are generally presumed to have the capacity and right to make free and informed decisions. Respect for persons thus means respecting the exercise of individual consent.”<sup>140</sup> These same principles serve as the foundation for both the Nuremberg Code and the Declaration of Helsinki. Both documents hold respect for the individual as sacrosanct. An examination of these codes brings into focus the myriad of issues involved in the ethics of clinical research.

**Table 4.1- Select Moral Codes**

<b>Select Codes of Requirements for the Ethical Conduct of Clinical Research</b>		
<b>Code</b>	<b>Source</b>	<b>Years and Revisions</b>
<b>Hippocratic Oath</b>	Antiquity (Greece)	Modern Versions circa 1964
<b>Nuremberg Code</b>	Nuremberg Military Tribunal	1947
<b>Declaration of Helsinki</b>	World Medical Association	1964, 1975, 1983, 1989, 1996, 2002

Although these documents seem to be of fundamental importance, some researchers deny their relevance or moral force. This is particularly true of the Nuremberg Code. Some have argued that this Code was simply a response to a unique set of deplorable conditions, which are irrelevant to modern day clinical research. I disagree with this assessment of the Code. The Nuremberg Code touches upon several important elements of clinical research, including the rights of the research subject and the obligations of the clinical researcher.

Although both the Nuremberg Code and Declaration of Helsinki address the ethical requirements of clinical research, the Hippocratic Oath does not. Some may claim that the Hippocratic Oath is not binding upon clinical researchers. This view may be supported by marking a distinction between the physician and the clinical researcher. This distinction is supported in part by the fact that they have different obligations and goals. The goal of clinical research is to answer scientific questions and develop medical interventions. The goal of clinical care is to treat the needs of specific patients. This distinction was discussed in the preceding chapter. Even if that dichotomy does not hold, it is clear that when one considers the ancient version of the Hippocratic Oath that many contemporary medical practices violate elements of the Oath. The Ancient version makes it clear that neither abortion nor euthanasia is permissible. The Modern version has similar prohibitions. The fact that several elements of the Oath are (at the minimum) ignored by many practitioners bears careful consideration.

Another important consideration is the difference between the ancient Hippocratic Oath and modern version or versions of the Hippocratic Oath. “According to a 1993 survey of 150 U.S. and Canadian medical schools, for example, only 14 percent of modern oaths prohibit euthanasia, 11 percent hold covenant with a deity, 8 percent forswear abortion, and a mere 3 percent forbid sexual contact with patients—all maxims held sacred in the classical version.”<sup>141</sup> If a physician has forsworn performing abortions by reciting an oath at his graduation ceremony, is he acting immorally when he performs one?

The relevance of the Hippocratic Oath to our discourse is this: The Hippocratic Oath is supposed to be part of the foundation for a physician's therapeutic obligation and his ethical responsibility to his patients. From this some have argued that doctors that engage in clinical research, particularly those who employ placebo control trials, violate their therapeutic obligation. They claim that doctors are violating a sacred principle of the art of medicine by proposing that patients engage in research activities that will not have a curative effect upon them.

Although some argue that the therapeutic obligations originates with the Hippocratic Oath, in point of fact, the statement "do no harm", is not contained in either the ancient or modern version of the Oath. The ancient version contains the phrase, "I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice." How such a statement is to be interpreted or applied in practice is certainly debatable. Further even if we could agree on an interpretation of the Oath and how it is to be applied in practice, there is a great disparity between the modern versions of the Oath and the ancient version.

Given that there is a not a uniformed statement of the Oath that is binding upon all physicians it cannot serve as a universal foundation of research ethics. That is not to say that doctors do not have obligations to their patients, but if those obligations are universal, they can't be based on statements, codes or oaths that are not. Even if there were such a universal statement, I am of the mind that oaths sworn at a graduation ceremony are not particularly important. How important is a professional oath? Should I feel better if my plumber has taken the plumber's

oath or my mechanic the ones for auto repair professionals? The importance of Oaths has been defended by others.

Daniel Sulmasy argues that Oaths are of great importance to practitioners who take them. He goes so far as to say, “Oaths bind persons to each other. An oath is an utterance of the form, “I swear to be X for you.” An oath is inherently interpersonal, creating a new reality between two or more persons.”<sup>142</sup> I am not sure that this position is tenable. If you consider the Hippocratic Oath, does it bind the physician to all of mankind? I am not certain that an individual can be in a meaningful relation of this kind with all of humanity. Beyond this the Hippocratic Oath does not fall into the schema that Sulmasy employs above. In the schema above X swears to Y, not as would be required to swear an oath to all of humanity: X swears to Y<sup>1-7billion</sup>.

Even if it did fall into the schema he employs, I am not certain that I know what it means to say that an oath creates “a new reality between two or more persons”<sup>143</sup>. Does a contract perform the same function? When I sign a cellular phone contract have I created a new reality between myself and AT&T?

I note Sulmasy’s views mainly because he has a reasonable discussion that highlights the differences between oaths, promises, and codes. He argues that “Oaths, like promises are performative utterances... Oaths are distinct from codes. Codes are collections of specific moral rules. Codes are not performative utterances. They do not commit future intentions and do not involve the personhood of the one enjoined by the code.”<sup>144</sup> He argues that oaths, unlike promises are never trivial, that they become a part of the person, and that oaths



prescribe consequences for those that break them. He thinks that oaths have more force than a promise.

When he says, “when one swears an oath, one’s words and one’s person become intertwined” he seems to mean that an oath is something that you are bound to keep, always. So in a sense, it becomes part of who you are. For example, in the case of the oath of marriage, one is proclaiming that they are now united to another individual, forever. Luckily, (in some cases), there are practices that allow one to break free of this eternally binding promise; there are procedures for renouncing oaths.

I believe that oaths are special kinds of promises. They are both, to employ Sulmasy terminology, “performative utterances”. I would argue that oaths are a sub-category of promises. The term promises seems to be broader than the term oath. If this is correct then it follows that an oath is a special type of promise. It is a promise to uphold certain basic standards in the performance of one’s duties or obligations.

As for the distinction between oath and codes, Sulmasy argues that oaths carry a greater moral weight; I disagree. Moral codes can carry just as much moral force as an oath. Many professional organizations adopt codes of ethical conduct. The AMA has a code of ethical conduct; in that case one could argue that it is binding upon all members of the organization. It does not seem reasonable to assume that all physicians are bound by the Hippocratic Oath because not every physician has actually taken the Oath, nor is there a uniform statement of the Oath. In my view a moral code can carry just as much moral force as an oath.

Ultimately in both cases, physicians and researchers disagree about the relevance and force behind oaths and codes.

Although many physicians have expressly consented to particular moral codes, are all physicians implicitly bound by moral codes, although they may have never expressed their consent to them? In some cases yes, and others, no. At Nuremberg, the Nazi doctors were judged and held accountable for actions that the tribunal felt violated the basic rights of their prisoners. (Prisoners again, that most likely had committed no crime beyond being different from the social norm.) The Nazis violated the basic rights of persons. Further, in these cases the physicians involved in these heinous experiments were also held to a higher standard because it was argued that they had an obligation to “do no harm” as stated in the ancient Hippocratic Oath. In this case they were “bound” by the Oath- one they may never have taken.

There is no doubt that their actions were deplorable. The Nazis were tried for crimes against humanity, in part because they were seen as violating a sacred trust between physicians and all of mankind. From where this sacred trust originates is an important consideration. During the Doctor’s Trial at Nuremberg the chief prosecutor, Telford Taylor proclaimed that, “This was no mere murder trial” because the defendants were physicians who had sworn to “do no harm” and to abide by the Hippocratic Oath. He went on to say that the people of the world need to know the rationale these doctors employed so that such ideas could be “cut out and exposed before they become a spreading cancer in the breast of humanity.”<sup>145</sup>

In the end, twenty-three doctors were tried in the case, sixteen were found guilty, and seven were executed. There is no doubt that they performed heinous acts, but they may not have violated any oath, code or codified law. In fact many claimed that they were just following orders and the current law of the Fatherland. I have no doubt that justice was served in this instance by their trial and punishment, but I would question the foundation of such justice. It most likely does not rest upon an ancient Oath.

In fact it should not be assumed that it is violation of the Hippocratic Oath that justifies the punishment of the Nazi doctors. As David Hume was apt to note regarding ancient contracts, “being so ancient, and being obliterated by a thousand changes of government and princes, it cannot now be supposed to retain any authority.”<sup>146</sup> Although Hume is referring to a social contract that binds man to certain social rules and institutions, there is an analogy between what Hume has in mind and the Hippocratic Oath. It, too, is an ancient decree, one that may have changed over countless generations, that supposedly binds physicians into performing particular duties. Is it not so old as to be no longer binding? One final consideration on this point: it is unclear how many of the Nazi doctors actually took the Hippocratic Oath. If they did not take the Oath, then they could not have violated it, as it is not possible for a person to violate an oath they have not taken.

A trial of this kind, conducted in an international forum, raises important questions about the basic rights and liberties of persons. It presupposes the concept of autonomy and the right of self determination that I argued for in the

previous chapters. A further implication is that in the absence of international law or positive law it appears as if persons still retain certain basic rights. I have argued that persons have certain basic prima facie rights, such as the right of self determination. It would seem that if this is the case then others have an obligation to protect and respect those basic rights. The right of self determination is a basic prima facie right. It is a basic liberty that all competent persons possess. Every person has the right to make choices and decisions that have bearing upon the nature and quality of our lives. It is wrong for others to impose their will upon our own, to use us as a means towards their ends. If pressed for a philosophical justification of these rights, I would argue that these basic human rights of persons are both negative and natural. In the case of the Nazis the international community proclaimed that, in the realm of medical experimentation, test subjects have certain basic rights that should not be violated.

As already mentioned, the first modern code of requirements for the ethical conduct of clinical research was articulated in 1947. The code was developed as the result of the atrocities perpetrated by the Nazi regime in Germany in the 1930's and 1940's. The Nazi's conducted all manner of inhumane experiments upon unwilling test subjects. After World War II these acts were brought to light, and the Allied Powers held a series of trials by the International Military Tribunal for War Crimes. One of those trials was known as the "Doctor's Trial". The trial focused on the actions of twenty-three leading German physicians and administrators. They were charged with war crimes and crimes against humanity.

Nazi physicians conducted numerous experiments and projects including the "Euthanasia" Program, the systematic killing of those they deemed "unworthy of life." The victims included the mentally retarded, the institutionalized mentally ill, and the physically impaired. German physicians also conducted medical experiments upon thousands of concentration camp prisoners without their consent. Most died as a result of these experiments. Others were scarred or crippled as a result. The victims included Jews, Poles, Russians, and also Gypsies.<sup>147</sup>

### **The Doctor's Trial in Nuremberg**

On August 19, 1947, the judges of the American military tribunal in the case of the USA vs. Karl Brandt et al. delivered their verdict. Before announcing the guilt or innocence of each defendant, they put forth what is now known as the Nuremberg Code. The magistrates in this case articulated the code in response to a perceived lack of guidance about the basic rights of experimental subjects. As noted earlier, these doctors may not have violated any oath or code. They may not have violated an existing national or international law either. Because there were not any clear international guidelines for the ethical conduct of human experimentation, the tribunal wanted to make sure that such a perceived ambiguity in the law could not be employed in any future cases.

Several Nazi doctors had argued in their defense that their experiments differed little from previous American or German ones. They were able to demonstrate that there was no international law or informal statement that differentiated between legal and illegal human experimentation.<sup>148 149</sup> During the

trial defense attorneys argued that “nations such as France, the Netherlands, Britain, and the United States had performed dangerous experiments on prisoners, often without their consent. They cited the American malaria experiments to argue that Nazi physicians had followed common research practices.”<sup>150</sup> Citing another wrong, does not make you right. The reality is that many of those experiments may have been unethical as well, but there is a legitimate issue about punishing German doctors for conduct that, in some cases, was deemed acceptable in America.

The Nazi doctors also employed another, more troubling, defense of their actions. “Defense lawyers explained that Nazi doctors were ordered by the state to conduct such experiments as the high-altitude, hypothermia and seawater experiments on inmates at the Dachau concentration camp to determine how best to protect and treat German fliers and soldiers. They contended that these experiments were necessary and that the “good of the state” takes precedent over that of the good of the individual.”<sup>151</sup> It is startling to see utilitarian arguments employed within this context. In chapter 2, I noted several problems with employing a Utilitarian defense of clinical trials. The Nuremberg Trials bring these problems into sharp focus; given this fact, I will briefly re-examine some of these issues here.

Could it be argued that utility was maximized by these actions? This question can be answered in various ways. The short answer is that this is a caricature of act Utilitarianism that has already been discredited. No reasonable philosopher would accept this as an ethically defensible application of the utilitarian maxim.

That answer may be too quick given the fact that these doctors engaged in their heinous experiments day after day. They methodically violated the autonomy and rights of their experimental subjects. These are the actions of individuals that surely must have examined the rationale for their experiments. They may have actually believed their actions were justified. Furthermore they may well have employed a twisted version of act Utilitarianism to do so.

The question of value is going to be raised at several times in this analysis of clinical research. What has value to a Nazi? From the Nazi perspective the life of Jew or a gypsy was a small price to pay for protecting the soldiers on the front lines. From a Nazi utilitarian perspective, even if he had considered the life of one of their prisoners to be equal in value to that of a German's life, he still may have sacrificed the prisoner to further his diabolical ends. If you can sacrifice a few in order to save the many, such a compromise may be compatible with the principle of utility. Not all versions of Utilitarianism would agree with this assessment, but it is certainly possible to develop a viable interpretation of the principle of utility that would consider such research to be ethically permissible.

Most utilitarians would take issue with the Nazi interpretation of their maxim. A utilitarian might argue that violating an individual's right of self determination can be justifiable if you consider the issue from the perspective of a short term calculation. Yet the action would fail to be justified if the long term consequences were correctly calculated. The long term disutility of systematically violating the autonomy and rights of individuals makes the action impermissible.

From the perspective of the patient, if the needs of society or all of humanity would truly be served by you subjecting yourself to clinical research, then a utilitarian patient might come to the conclusion that it is morally obligatory for them to participate in the research. In this particular case, in a Nazi concentration camp, I doubt any of the persons employed by the Nazis would have arrived at this conclusion.

### **Refutation of Nazi Utilitarianism**

Common sense might lead one to dismiss the Nazi claim out of hand, yet given the scope of their actions and the depth of their evil, I think that is a mistake. The notion that the end justifies the means is all too common a theme throughout history. (In fact it is still employed today to justify conducting experiments upon individuals without their informed consent!) It should be addressed head on and then dismissed as false. It is one thing to say that we should maximize the greatest good and then take the next step by requiring a person or persons to actually act in that way. Is it ethical to “obligate” a person to do X just because it creates the greatest good? This is one of the classic problems or counter-arguments against the greatest happiness principle. Consider the case of torturing one child for all eternity so that the rest of humanity could live in peace; it would seem that the net loss to the child is outweighed by the net gain in utility by all of humanity. Most opponents (and utilitarians) would deny that this is an ethical course of action. But given the tenets of Utilitarianism one could argue that since the greatest number of people have the greatest good then we could justify such an act.



Utilitarians endeavor to counter this argument but most of their arguments seem rather weak and inconsistent with their principles. Again, as noted in chapter 2, it looks as if the Utilitarian determines first if there is a net gain in utility in the short run and then decides on intuitive grounds if the act is immoral. If it is seemingly immoral, then we say: sorry, there will be a loss of utility in the long run. If it looks okay from a moral point of view, then we do not say this. But, then, is the Principle of Utility really being used to decide things? I think the answer is no. The utilitarian will deny this, but then the onus is upon them to provide a satisfactory rationale for their claims regarding how the principle of utility is to be applied in these cases. In most cases they beg the question against anyone that supposes rights and interest of individuals are more important than utility.

I think that the rights of persons are more important than how they can be used to achieve a goal. I think they should have a say as to whether or not they want to participate in a given activity- regardless of how useful, beneficial or pleasurable it may be. Ultimately, Utilitarianism is not a good foundation for the ethical analysis of clinical research. There is no legitimate philosophical justification, utilitarian or otherwise, that can provide an adequate defense for the actions of the Nazis.

### **The Nuremberg Code**

The Nuremberg Code (in its current form) has ten principles. When originally presented during the judgment phase of the Doctor's Trial it contained six principles. Most of these requirements address either the basic rights of the

research subject or the corresponding obligations of the clinical researcher. These principles are compatible with the minimalist approach that I have defended to this point. It has been said that, “the Nuremberg Code is the most important document in the history of the ethics of medical research.”<sup>152</sup> I tend to agree with that assessment of the Code’s importance.

Some commentators have argued that it was a response to a unique situation, and that it has no binding force or relevance to modern research ethics. In my view, this is a mistake. I believe that the Nuremberg Code serves as an important foundation for the rights of research subjects. I think that most of the rights and obligations stated within the document are fundamental to conducting ethically permissible clinical research. By the same token, each principle must be explained and justified by a coherent theoretical system. It is not enough to simply claim these rights and corresponding obligations; one must argue for them.

The first (and arguably most important) principle stated in the Nuremberg Code is that of “voluntary consent”. The principle says, “The voluntary consent of the human subject is absolutely essential.” There will be a limited number of cases where informed consent cannot be obtained because the subject is not old enough or competent to consent. In these cases the research may be ethically permissible if consent is obtained from the guardian of these individuals. Yet, in my view, in cases where consent can be obtained, it should and must be obtained. Research conducted without consent is unethical.

Some argue that this would limit certain types of research, such as that aimed at promoting public health or emergency room care. I agree that it would make it

more difficult, in some cases, to conduct research in these setting, but I think that our right of self determination is of such paramount importance that respecting it must take precedent. Perhaps more time and thought should be spent by these critics of informed consent and our basic rights in developing studies that do not violate these fundamental principles. It certainly would be easier to conduct research if we never needed informed consent. Imagine the leaps in scientific progress we could make if scientist and doctors could enroll people in clinical research as they deemed fit. Such a situation would most likely result in dramatic medical and scientific gains, yet it would come at the expense of one of our most fundamental and basic rights- the right of self determination. In such a situation you need up violating the basic rights of those you intend to benefit.

Returning to the Code, it has an important provision which is found after principle 1. It says in part, “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.”<sup>153</sup> The elements involved in obtaining informed consent are often overlooked in present day research. This point relates to the question of whether or not the subject is actually “informed”. The experimenter, who may not be the one to actually obtain consent, cannot assume that it has been obtained before he employs someone as a subject of clinical research. Consent is such an integral element to the ethical permissibility of clinical research, that as a practical matter, it ought to be reviewed by the person conducting the experiment before the subject is experimented upon.

Although most of the code is pertinent to the discussion of ethical permissibility, I will restrict my analysis to those principles which I consider to be essential. There are several parts of the code that discuss the value and validity of the research being conducted. The sixth principle states, “The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”<sup>154</sup> In other words, the risk involved in the experiment should never outweigh the potential gain to humanity. Important, life saving research allows for the ethical permissibility of experiments that carry with it significant risk. In general, I think this is an important consideration. Life and limb ought not to be put in harm’s way in order to develop the latest acne cream; yet by the same token, if the individual subject believes that this is a legitimate endeavor, then he should be allowed to partake in the experiment. The right of self determination allows people the liberty to scuba dive, sky dive, ride bikes off of cliffs and enroll in dangerous clinical trials.

One feature of many moral codes is that they often contain paternalistic elements. The principle mentioned above could be interpreted in a paternalistic way. As stated it is somewhat ambiguous. It does not clearly delineate who is to evaluate the nature of the risk involved in the experiment. In my view the physician should endeavor to explain the potential side effects and risks involved with the research to the patient. The physician should also explain the potential benefit to the subject (and to humanity) so that the subject may make the final, informed determination about his participation in the research. Neither the

researcher nor some other review board ought to make the final determination or choice for the subject.

An essential element of respect for persons is respecting their right of self determination, their autonomy, and their right to participate in clinical trials. Paternalism, in the sense of protecting potential experimental subjects from themselves is unacceptable and unethical. Stopping an experimental subject from making the decision to enroll in clinical research is not compatible with respect for his right of self determination or his individual autonomy.

Principle 9 of the Code says, “During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.” The notion of free participation and free withdrawal is essential to respect for the right of self determination. In abstract, when looking at an informed consent agreement or a study protocol, it may be difficult to understand the pain or discomfort actually involved in the clinical trial, as such an experimental subject ought to have the right to withdraw from the study at any time. I would add the following caveat: That a subject should be free to withdraw at any time so long as the subject’s withdrawal can be accomplished safely. In some studies it may be dangerous to the subject to simply stop in the midst of the trial. They may have to be gradually weaned from the study drug.

The final principle for consideration, principle 10 says, “During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the

good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject". The rationale behind this principle is that sometimes an experiment must be stopped when dangerous, unforeseen side effects are discovered. I think that this is an important consideration. Prima facie, this might seem like paternalism; I would argue that it is not.

When conducting an experiment, the researcher is the expert. If the researcher determines, based upon data collected or some new information, that there are dangers inherent to the continuation of the experiment, then he should stop the experiment. The patient should be informed of the new dangers associated with the experiment and then be given the option to continue in the experiment- if this is feasible. It may not be feasible, because a significant number of test subjects may choose to withdraw thereby invalidating the results of the experiment. If the experiment will not be scientifically valid, then there is no reason to continue.

### **The World Medical Association's Declaration of Helsinki**

Given the atrocities performed by the Nazi doctors, ( and the fact that that the Nuremberg Code stated that voluntary consent was necessary in all cases, thereby excluding research on any group that could not give consent) the WMA felt that there was a need to provide physicians worldwide with recommendations to guide them in biomedical research involving human subjects. After nearly a decade of discussion and research, a draft of the Declaration was prepared. This draft, originally tabled in 1961, was examined and revised several times until its final adoption at the 18th General Assembly in Helsinki, Finland in 1964.<sup>155</sup>

The Declaration has been modified five times, the most recent in 2000. Two notes of clarification have been added, the most recent was in 2004. In an interesting aside, the FDA does not recognize the current draft of the Declaration. The FDA is employing an earlier draft of the Declaration to evaluate research conducted outside of the United States. The fact that the FDA has withdrawn support for the Declaration raises significant questions about its legitimacy. It is often assumed, by those that hold the Declaration as a foundation for ethical research, that it is universally accepted and/or binding. The reality is that it is not. This is another reason to look elsewhere (other than either the Nuremberg Code or Declaration of Helsinki) for the ethical permissibility of clinical trials. The FDA requirements for research conducted in the United States will be considered in the next chapter.

The Declaration is aimed at both practicing physicians and clinical researchers. As noted above, the principles stated therein are supposed to apply universally to all who are conducting clinical research. It is unclear whether or not this is actually the case given that several countries have failed to endorse particular drafts of the Declaration. There has been much debate about these matters. In particular there has been a great deal of criticism of the 2002 and 2004 “notes of clarification” that involve the use of a placebo control. Benjamin Freedman, Kathleen Glass and Charles Weijer claim that, “The Helsinki statement is badly worded as a statement of medical science or of ethics. It seems to rest on dubious assumptions: that at some defined point treatments are proven, and that for a given population we can scientifically identify a single best diagnostic and

therapeutic method... considering the uncertainties of medical science and the heterogeneity of patient populations, it is rare for the medical community to be in accord as to which treatment is the best.”<sup>156</sup> Although they are attacking the Declaration, they are also making an important point related to the notion of equipoise. Some commentators maintain that RCTs are only ethically permissible when there is a state of equipoise. This same concept is termed the “uncertainty principle” in many European journals.<sup>157</sup> According to Benjamin Freedman, “The ethics of clinical research requires equipoise--a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial”<sup>158</sup>. In his view, there must be genuine uncertainty about which treatment is the best, but given what he says above, uncertainty is a rather common state of affairs in the medical community. If Freedman is correct, then even if equipoise is necessary, (which I deny), it should not be problematic for most clinical trials to meet this condition. (For a full discussion of this concept, please see chapter 3, page 146.)

The current version of the Declaration of Helsinki contains 32 principles divided among 3 sections: A) Introduction, B) Basic principles for all medical research, and C) Additional principles for medical research combined with medical care. The Declaration claims to be binding upon all the physicians of the world. It claims that all physicians have certain moral obligations and that patients have certain universal rights. The most basic of those obligations is “to promote and safeguard the health of the people.”



The WMA believes that this also entails improving the medical arts by engaging in clinical experimentation. Principle 4 says, “Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.” The nature of the methodologies to be employed when conducting such research has engendered a great debate. As noted in the preceding chapter, some have argued that placebo control trials (PCTs) are not compatible with the principles stated in the Declaration or the obligations of physicians in general. Before discussing the issue of placebo controls, I will consider some important implications of the principles stated within the Declaration.

**Principles That Stress the Importance of Personhood, the Right of Self Determination, and Individual Autonomy**

The Declaration contains several principles that stress the importance of respect for personhood and the right of self determination. Both Principle 10 and 22 are compatible with and support my assertion that the right of self determination and informed consent provide the foundation for ethically permissible clinical research. Principle 10 says, “It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject”<sup>159</sup>. This principle applies to the physician within the context of clinical care as well as the physician in the context of clinical research. Principle 20 says, “The subjects must be volunteers and informed participants in the research project.”<sup>160</sup> Within the context of clinical research voluntary consent is of the utmost importance. Yet unlike the Nuremberg Code, which begins with this

principle, it is buried towards the end of the Declaration. I think that this principle should take a more prominent role in the Declaration.

The application of principle 10 has engendered a great deal of debate. Opponents of clinical trials, particularly those conducted in the developing world often question whether such experiments “protect... the dignity of the human subject” involved. Also there are several trials that are conducted without obtaining informed consent. The FDA regularly allows such trials to be conducted. It would seem that all of those trials violate principle 20. These considerations will be explored in detail below.

### **Principles of the Declaration that Raise Concerns for the Ethical Permissibility of Clinical Research**

As noted earlier the Declaration contains 32 principles. Yet taken together, it is not altogether apparent that the document is internally consistent. It does not seem that all of the principles can be satisfied at the same time. If this is the case, then which principles are binding upon the researcher in which situations? Consider principle 20: *The subjects must be volunteers and informed participants in the research project.*<sup>161</sup> Is it possible for subjects that are not competent to satisfy this principle? It would seem that children or those not competent to consent cannot meet this condition. To that end, the Declaration contains two further principles, 25 and 26 which address this issue:

Principle 25: When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.<sup>162</sup>

Principle 26: Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents

obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.<sup>163</sup>

Unlike the Nuremberg Code which explicitly states that “the voluntary consent of the human subject is absolutely essential.”<sup>164</sup> The Declaration allows for the possibility of research conducted upon populations of individuals that cannot consent to research. Interpretation of the Declaration can be a difficult enterprise.

Although it has been lauded for expressing the guiding ethical principles of clinical research in 32 principles that run about 2000 words, the Declaration of Helsinki is a document that betrays evidence of being written in committee. It is clear that it is designed to protect the competing interest and needs of those who created it. Physicians have a stake in furthering their medical knowledge, and they need human subjects to fulfill that end. As such there exist a prima facie conflict between furthering knowledge of medicine and treating individual patients.

Another important issue for consideration is raised by Principle 19 which states, “Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.” Is this principle really necessary for clinical research to be ethically permissible? Is it wrong to experiment on particular populations but then not provide them with the opportunity to enjoy the medical interventions developed as a result of their participation in the research?

Research conducted in developing countries seems to violate this principle. This appears to be the case for research conducted in developing countries where most of the population will never receive the treatments nor have the economic resources to purchase the interventions developed there. It appears that entire populations are recruited to be experimental subjects yet stand little or no chance of ever benefiting directly or indirectly from the results of this research. Research that is conducted and interventions that are developed in these regions seem to clearly violate Principle 19. Several commentators have made similar objections.

From 2000 till 2001 a Placebo Control Trial of nitazoxanide was conducted on children in Zambia, Africa.<sup>165</sup> The trial was conducted to test the effectiveness of nitazoxanide in treating a parasite known as *cryptosporidium parvum*. *Cryptosporidium parvum* is an important cause of diarrhoeal disease in children and adults in developed and developing countries, and of large waterborne outbreaks in developed countries.<sup>166</sup> In this study there were four cohorts of patients. 50 of the patients had HIV, 50 did not. Each group of 50 was either randomized into the placebo arm or given the study drug. The dose of the study drug was insufficient to cure any of those children which had the parasite who were also infected with HIV. Although some of the children in this study benefited by being randomized into a treatment arm of the study, and were cured of their parasitic infection, 75% were not. The children randomized into the placebo arm received no treatment, and most of them died.

Even if we accept the claim that the children that were randomized into the treatment arm benefited from their participation in the study, once the researchers

left, and the trial was finished, those children had no hope of receiving future treatment. Nor did any other members of their community have but the remotest chance of future benefit from the intervention developed. There is no “reasonable likelihood” that these people will ever benefit from the research conducted in their community. Western scientist used the people as a commodity, and left when their experiments were finished. These people were a means to an end, no more and no less. These actions may be entirely compatible with a utilitarian analysis of this situation. A new medical intervention was confirmed, at the expense of a 100 people. Millions may benefit, 50 were sacrificed to the placebo arm of the study. Are these actions compatible with Principle 19? Are these actions ethical, (even if we deny the moral significance of the Declaration of Helsinki)? In my view, if they understood the risk and benefit involved- which is debatable, then the trial is ethical.

This study is similar to others that take place on a regular basis around the world in developing countries. According to Sonia Shah author of the book, *Body Hunters: Testing New Drugs on the World's Poorest Patients*, “Just 0.3 percent of the drug industry's much-touted R&D resulted in the handful of drugs approved for tropical diseases between 1975 and 1997, despite tens of thousands of industry-sponsored clinical trials conducted around the world every year. Currently, US companies are investigating treatments for oral cancer in China, lupus in Mexico and severe short stature in Eastern Europe, among other studies-- not exactly a list of the world's most pressing public health problems.”<sup>167</sup>

In the vast majority of these cases, the local populations that are employed as guinea pigs by pharmaceutical corporations stand little chance of any likelihood of benefit. Do all of these studies violate principle 19? I think the answer is yes. For the sake of argument, let us assume that some of the Principles found within the Declaration of Helsinki are binding in certain cases, but not in other, so that not all 32 must be satisfied in all in order for research to be ethically permissible. So if we are to take this weaker interpretation that only relevant principles need be satisfied in order for clinical research to be ethically permissible, then this particular principle still raises concerns for trials conducted in this manner. Specifically it raises concerns for research conducted in developing countries. If this is the case, then either principle 19 is not necessary or, if it is, most research conducted in developing countries fails to satisfy this principle and should be judged ethically impermissible. This point seems to have been overlooked or ignored by many commentators of the Declaration but not all.

Participants in the 2001 Conference on the Ethical Aspects of Research in Developing Countries created a document called, “Moral Standards for Research in Developing Countries.”<sup>168</sup> This group argues that the notion of “reasonable availability” ought to be replaced by what they term “fair benefits”. They argue against the conception of reasonable availability, by saying, “First, it embodies a very narrow notion of benefits. It suggests that only one type of benefit--a proven intervention--can justify participation in clinical research. But a population in a developing country could consider a diverse range of other benefits from research,

including the training of health care or research personnel, the construction of health care facilities and other physical infrastructure...”

I think that this interpretation misses the point of Principle 19. The rationale is that under-privileged groups should not be systematically employed as research subjects. It is not that their services as research subjects ought to be paid for by providing them with new infrastructure or other commodities beyond the medical interventions developed. This group of researchers seems to recognize that Principle 19 entails that experimental subjects ought to have the prospect of some benefit from participating in the research, but it does not follow that they ought to receive what they term a “fair benefit”. This is because they build into the term “fair benefit” features that may not be necessary for the benefit to actually be fair to the groups employed.

Their use of this term is misleading because a “fair benefit” may not actually result in a fair benefit to the individuals involved in the research. The fact that a community gets a new hospital because my child was an experimental subject may not be a fair benefit to me or my child. An example of a fair benefit would be giving me access to the medicine that was developed to help alleviate my condition. This group is trying to turn the principle of reasonable access into a social good. I think this is a poor way of interpreting Principle 19 of the Declaration- one that is misleading.

Another section of the Declaration that raises ethical concerns for many studies is Principle 22. This principle says in part:

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.<sup>169</sup>

One could legitimately argue that this principle is systematically violated by research conducted in the United States.

As noted earlier many physicians recruit subject from their private practices. Seldom, if ever, do they inform the patients that they have a financial stake in their enrolment in the research trial. How is it legitimate for doctors to receive huge signing bonus for recruiting their patients into clinical trials? Clearly this is a conflict of interest. If it is unethical, (at least according to the FDA), to use money to “unduly” influence potential test subjects into participating in research studies, then should this same logic not apply to physicians? Can they be “unduly” influenced into recruiting patient into clinical trials? If so, this practice of paying physicians a “finder’s fee” for enrolling their patients in trials should be abolished. As discussed in an earlier chapter, research conducted in this manner seems to create a conflict of interest between the physicians and their patients. The close association of clinical care with clinical research leads to situations where the rights of patients are easily (and systematically) violated.



### **The Declaration of Helsinki and Placebo Controls**

The principle that has garnered the most criticism is principle 29 and the note to principle 29. Principle 29 says, “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.” As stated this principle seems to exclude Placebo Control Trials in situations where there already exists a proven therapy. This principle has fueled the debate already examined about the ethical use of placebo controls.

At this juncture I will not revisit the argument for and against the use of a placebo control, but the WMA attempted to clarify the situation by adding the following “Note of clarification on paragraph 29 of the WMA Declaration of Helsinki”:

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.<sup>170</sup>

Why has the WMA taken such a stand? Is it pandering to the pharmaceutical corporations? As mentioned earlier, physicians have a vested interest in

improving the art of medical practice. Clinical research is essential to that end. As argued in chapter 1, Randomized Control Trials with a placebo control are necessary to confirm the efficacy of most interventions. There is a compelling epistemic and scientific need for the use of a placebo control. It is the surest way to test and confirm the efficacy of a medical intervention. This view has been dubbed “placebo orthodoxy” (as opposed to active control orthodoxy or observational orthodoxy).<sup>171</sup> It has also been called a myth. I hope that I was able to argue convincingly that it was not a myth when arguing for the PCTs the epistemic necessity in a previous chapter. The ethical struggle is to balance the rights of the individual with the goal of science (the betterment of mankind). Hans Jonas went so far as to argue against the requirement for scientific advancement. He said that the “melioristic” endeavor of advancing medical sciences does not obligate us to conduct clinical research. Our progeny, the future generations of humanity have the right to demands air to breathe and water to drink, not advances in science at the expense of our souls.<sup>172</sup>

The footnotes to Principle 29 allow for PCTs where there is minimal risk or “Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.” This clause can be used to argue for a PCT in most cases, as most, but not all researchers argue that *is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method*. The debate about the ethical use and epistemic need for the placebo control may go on without end. It

is not helped by studies, such as those run in Africa, where many experimental subjects are sacrificed for new medical interventions.

### **The Ethical Significance and Philosophical Analysis of Moral Codes and Oaths**

As mentioned above, which, if any, codes or oaths are binding upon individual researchers? Although the WMA presumes to speak for the world's physicians, this is not the case. Several countries have withdrawn membership from the WMA on various occasions in order to make political statements. Although most are members, membership is not universal. Beyond this, there is not a universal interpretation of the Principles. Further, even if we could agree that a particular code was binding, are we to assume that all the principles must be satisfied in order for clinical research to be ethically permissible? This seems difficult as there is at the minimum a tension between several of the principles, if not an outright logical improbability of certain of the principles holding together- some of them seem mutually exclusive.

Both the Nuremberg Code and Declaration of Helsinki contain statements that research should be stopped if new data is obtained during the course of the trial that dramatically increases the risk to the experimental subject. In practice this does not always happen. Consider the case of Ellen Roche. In June of 2001 Ellen Roche died as a result of a clinical trial conducted at Johns Hopkins University. She was one of several test subjects to receive a new compound for the treatment of asthma. She was a healthy volunteer employed to test the pharmacodynamics and pharmacokinetics of the compound. The first test subject had a mild reaction.

The second reported no side effects, as the third subject, Ms. Roche had a severe side effect which ultimately lead to her death.

In an external review of the case, it was determined that the study participants had not been adequately informed of the potential, life threatening side effects of the study drug. Further it was argued that the study should have been stopped after the first patient reported side effects. In this case, Ms. Roche died for \$365. If she had completed the study that is the amount of compensation she would have received.<sup>173</sup> Ironically both the Nuremberg Code and the Declaration of Helsinki prohibit the continuation of experiments where new data obtained during the course of the experiment indicates a dramatic increase in the risk associated with participating in the experiment. Unfortunately, though the researchers involved would most likely admit that they were at a minimum bound to follow the Declaration of Helsinki if not the Nuremberg Code; they did not apply the principles put forth in either document. In the end these moral codes did not save this young woman's life.

Franklin Miller argues that the Declaration has conflated the ethics of clinical care with the ethics of clinical research. He maintains that the ethics of clinical care are guided by four principles: autonomy, nonmaleficence, beneficence and justice.<sup>174</sup> He denies that all four principles apply to clinical research. As he says, "Given the purpose and characteristic methods of clinical research, it is misguided to treat clinical research as governed by the principles of therapeutic beneficence and therapeutic nonmaleficence. Clinical research, which is not aimed at personal medical benefit, would be impossible if all the risk of research interventions had

to be justified by their potential benefits for participants. These differences in purpose and method make risk-benefit assessment significantly different in clinical research than in clinical medicine.”<sup>175</sup> Miller maintains that because there is risk in research, and seldom direct benefit to the research participant, that the principle of therapeutic beneficence and nonmaleficence would systematically be violated if they were applicable to clinical research. He goes on to argue that it seems unreasonable for a moral code of research to make most research ethically impermissible. This same notion is applicable to both the Nuremberg Code and Declaration of Helsinki. It seems unreasonable to think that either document should be applied in such a way that most types of clinical research would be unethical.

With due consideration, I think that the Nuremberg Code captures most of the essential principles required to conduct ethically permissible clinical research. It articulates the rights and liberties inherent in the individual as well as the obligations and responsibilities of the clinical researcher. I feel that the Declaration of Helsinki originally expanded upon many of the considerations put forth in the Code, but some of the recent changes call into question its legitimacy (or primacy) as a universal statement of experimental subject protections. As stated earlier, moral codes can be employed as part of the ethical analysis of clinical research, but they are not the final word.

## **Chapter 5: Ethical Analysis of FDA Requirements for Clinical Research**

In this chapter I will examine the basic requirements mandated by the FDA when conducting clinical research. I will begin by examining the FDA mandated requirements, the IRB system, and the phases of clinical research. Each of these topics raises important ethical considerations. There are several issues to be considered, including the philosophical foundation of the FDA requirements, the ethical permissibility of the FDA waiver of informed consent, payment of experimental subjects, the phases of research studies, and the use of vulnerable populations. Although it might seem obvious that informed consent should be received before experimenting upon a subject, (especially when the subject has the capacity to give consent) this has not always been the case.

Even with regulations, studies are still conducted, in accordance with the FDA regulations, without obtaining informed consent. One of the most recent of which took place from 2004- 2006.<sup>176</sup> In 27 cities across the United States, seriously injured accident victims were used as experimental subjects in a Randomized Control Trial. The trial was testing an artificial blood substitute known as Polyheme. These people were enrolled in a trial and experimented upon without their knowledge or consent.<sup>177 178</sup>

Epistemically this type of research may be required in order to test the efficacy of a treatment, but ethically this type of experiment is not permissible. In general, I hold that research that violates certain basic principles, such as the principle that one ought to respect the rights of the experimental subject, is always unethical. If

research is unethical, then regardless of its epistemic worth, it should not be conducted.

If a researcher wants to test artificial blood, for example, then instead of testing on accident victims, request consent from patients undergoing non-emergency surgery. Certainly that would include a wide population of people upon which to test the product. This case will be discussed more fully below; as it stands, this trial was unethical and should have never been permitted to run because it violated the fundamental ethical requirement of informed consent. It is a violation of both the personhood and of the right of self determination to experiment upon an individual without his consent. If it is not a violation of our rights, then we are left with the absurd conclusion that anyone, at any time, may be employed as an experimental subject; this idea is explored in the new television shown *Fringe*- the world is one huge laboratory, and we may, at any time, be used as lab rats. I argue that regardless of the scientific or epistemic need, the rights and liberties inherent to persons should not be violated to further scientific ends. Research of this type is unethical.

### **Ethical Analysis of the Belmont Report**

What is known as the Belmont Report was developed in part as a result of the public backlash to the Tuskegee Syphilis Experiment. From 1932 till 1973 the United States Public Health Service conducted a clinical study without informed consent on African American sharecroppers that had syphilis.<sup>179</sup> This study was sanctioned by the United States Government and continued for decades; even after a cure for the disease was developed. The cure was not administered to the

study participants, even after its efficacy had been acknowledged by the medical community. The experimental subjects believed that they were receiving treatment for their condition, when in fact they were not. The researchers were simply recording the progression of the disease. Persons afflicted with syphilis eventually go blind and sometimes insane. Most of the subjects were deceived into thinking they were receiving treatment. Public awareness of this study (and other ethically objectionable research) eventually led to the Belmont Report which in turn led to greater oversight and regulation of clinical research.

The Report was developed by a special presidential commission. Its official title is *The Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*. The Report emphasizes a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles. The Report served as the foundation for the FDA Common Rule, Title 45 (public Welfare) and Title 46 (Protection of Human Subjects).

In 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral



research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.<sup>180</sup>

The Report has three parts: A) Boundaries between Practice and Research; B) Basic Ethical Principles; and C) Applications (of the ethical principles). The Report begins by differentiating research from practice. According to the Report, the term ‘practice’ “refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.”<sup>181</sup> Whereas the term ‘research’ denotes, “an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).”<sup>182</sup>

As has been noted in previous chapters, the lines between clinical practice and clinical research are often blurred. This usually happens when physicians conduct research within the same setting that they practice clinical care. This can lead to a conflict of interest. The goals of patient care and of clinical research are often at odds with one another. The patient must be made fully aware of the difference between clinical care and clinical research. The patient should not be suffering from the therapeutic misconception. In brief the therapeutic misconception is the idea that the experimental subject will benefit from clinical research, if, in fact, he will not. As I argued in a previous chapter, if informed consent is properly

obtained, then the experimental subject should not be suffering from the therapeutic misconception.

Even in settings where physicians are not conducting clinical trials with their patients, there is a measure of trial and error in the practice of medicine. Some patients respond to particular treatments, others do not. A physician must try new and innovative therapies from time to time, this might broadly be construed as experimental, but it is not the same as a clinical trial. The goal of clinical care is treating the patient; the goal of clinical research is to conduct experiments to confirm the efficacy of new interventions. These divergent goals are often in conflict. The observational evidence collected from clinical practice might form the basis for conducting further, detailed, trials of a particular intervention.

According to the Report three basic principles are relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence, and justice.<sup>183</sup> The principles serve as the basis for ethically permissible research in the United States. I feel that the first principle, respect for persons is the most important of the three. I will consider each below.

#### **Analysis of the Belmont Report requirement of “Respect for Persons”**

According to the Report, respect for persons consists in meeting the following requirements: Respect for persons incorporates at least two ethical convictions: first, that those individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the

requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.<sup>184</sup>

As was noted in a previous chapter, there is great ambiguity as to the meaning of the terms autonomy and freedom. In the quote above the authors use the term “autonomy” in a sense that is different from how I have employed it. I have argued that autonomy is a trait inherent of competent persons. It is part of the basis for our freedom and ability to make choices and take control of our life. The right of self determination, on my view, consists in one being at liberty to act in accordance with his beliefs and desires.

David Hume employs a similar definition of liberty. He defines liberty as *“a power of acting or not acting, according to the determinations of the will”*<sup>185</sup> One’s liberty is violated or restricted when another imposes his will upon yours. It is also violated, when someone else endeavors to make decisions for us. One interpretation of his views is that an individual is exercising his right of self determination by being able to act according to the determinations of his own will.

In the case of clinical research our autonomy is respected when we are allowed to choose of our own volition to participate in a clinical trial. In order to meet the requirement of informed consent, the researcher must provide the potential experimental subject with the pertinent information regarding the risk and benefits of participation. After this is done, the experimental subject is in an epistemic position to make an “informed” choice. If the person is competent, and properly informed, then he has made an autonomous decision. The researcher respects his

autonomy and his right of self determination by allowing him to make the choice. A person's rights and liberty can be violated in the following situations: If the researcher makes the choice for him, does not provide the requisite information, or coerces him into participating. In such cases the researcher has not respected his autonomy. All of these actions, on the part of the researcher, are unethical.

In the first instance the researcher has not allowed the patient to make a choice. The researcher has taken the decision out of the patient's hands by simply enrolling him in the study regardless of his wishes. An example of this type of ethical violation is found in Polyheme clinical trial. Again, in this clinical trial persons were employed as experimental subjects without their being informed of this fact or requesting their consent. I would argue that their right of self determination, (their right to choose what is to be done with their person), was violated because they were not given the choice to decide whether or not they wanted to enroll in the clinical trial. In this trial accident victims were randomly chosen to receive a potentially life threatening blood substitute. The researchers made this choice for them, in part, to further their own ends.

In the second case, the researcher withholds or provides misleading information about the risk and the benefit inherent to the study. The experimental subject's autonomy and rights have been violated because he made a decision under false pretenses. Perhaps if the subject were told the true nature of the risk, he would not enroll in the study. In this case the subject believes he is making an informed decision, when in fact he is not. Deception on the part of the researcher violates the rights of the experimental subject.

In the final situation, the experimental subject is forced to participate in research he would not otherwise enroll in. In this case the researcher says, “Enroll in this study or else I will inflict some harm upon you.” In the case of coercion, our autonomy has not been respected and our rights have been violated.

For example, if Dr. Hwang Woo-suk demands, “Give me your ovum or I will fire you from your research position”, to one of his young lab assistants, and she acquiesces then it is proper to say that she was coerced. The doctor has violated the young woman’s autonomy by placing such a demand upon her person. He has limited her liberty, by limiting her choices. In coercive situations this is done unjustly. In coercive situations our capacity to act autonomously is not respected and our right of self determination is violated.

As Wilkinson and Moore point out, “Coercion is paradigmatically a case of the denial of autonomy, since it consist in the deliberate imposition of one person’s will one another.”<sup>186</sup> The doctor does not have a right to demand such a thing of the young woman. He has placed her in a situation where she must choose between the lesser of two evils, neither of which are justified. He has tried to force her into a situation where she must make a choice that is one that she would not otherwise make. As stated above, her rights have been violated.

With regards to the wording of the Belmont Report the use of the terminology “diminished autonomy” can lead to confusion. I would argue that either people have the capacity to act autonomously or they do not. If they are autonomous then they are competent to deliberate and reach a reasonable decision regarding

their participation in a trial. Children, and those that cannot rationally deliberate, are not able to act autonomously.

In the case of autonomy you either have it or you do not, but it is not something that comes in degrees. As such, it cannot be “diminished”. It is either the case that you have the capacity to exercise what I have termed “the right of self determination” or you do not. What the authors most likely mean by “diminished autonomy” is an inability on the part of the person to make a competent decision.

Another possible interpretation is that they are conflating ‘diminished cognitive ability’ with ‘autonomy’. Consider the case of dementia. There are standardized examinations that can be employed to determine the extent of cognitive impairment. A patient can be diagnosed with mild, moderate or severe dementia. One might argue, based on the empirical evidence, that there are degrees of cognitive function and impairment. Assuming that cognitive function is tied to rationality this would seem to entail the thesis that there are degrees of rationality.

Rationality seems to be essential for persons to exercise their autonomy and their right of self determination. Part of the reason for claiming that children are not autonomous beings is that they lack a full understanding of the consequences of their actions. They are not able to perform rational deliberations and determine what is, in fact, in their self interest. In short, they are not rational. They may have the potential for rationality, but they are not rational at present. It seems that this is something that changes with time.

It is true that if one does not have the capacity (ability to reach a rational decision) to exercise his right of self determination, then he cannot enroll in clinical research. The right of self determination and the capacity to give informed consent seem to be essential components of ethical clinical research. A competent person must have the ability, in principle, to reach a rational decision; those beings that lack this capacity are not autonomous agents.

Each competent person should be respected and treated as an autonomous agent. Such people should be allowed to participate in or choose to refrain from clinical research. By the same token those individuals who are not competent must be respected as well. But respect in the case of those that are not competent (and thereby not able to exercise their right of self determination) means they should be protected. Those individuals who are not competent to consent to clinical research ought to be protected as much as possible from the risk inherent in clinical research. They should not participate in such research unless there is a prospect of direct benefit for their medical condition.

In cases where the patient is not competent to consent, then every possible measure ought to be taken to ensure that his rights and interests are protected. Research upon individuals that are not competent to consent should be limited, restricted, and regulated.

In general, regardless of a person's competence, the physician should not presume to have the authority or right to enroll patients in clinical research without their knowledge or consent. Likewise the physician should not presume to have the authority to exclude them (without justification) from research either.

This is consistent with my earlier criticism of review committees, because in a circumstance where an individual is not competent to consent to research a measure of paternalism is necessary and required. Although I have argued against paternalism, in cases where one is fully competent, I think it is necessary in cases where an individual is not.

### **Analysis of the Belmont Report requirement of “Beneficence”**

The Belmont Report goes on to discuss a second ethical foundation of research, beneficence. According to the Report, “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 not harm and **(2)** maximize possible benefits and minimize possible harms.”<sup>187</sup>

A statement as simple as “do not harm” can lead to a great deal of debate. Does randomization lead to harm? What about the use of a placebo? If the statement, “do no harm” is interpreted in a strong sense, then both randomization and the use of placebo could lead to the harm of experimental subjects with conditions that will worsen by being given a placebo or inferior treatment. In some cases this harm will only be temporary, but in other cases it could lead to permanent injury.

In a recent case a patient with moderate asthma was randomized into a placebo control whereby she was taken off medication during the course of the trial. Because she was given a placebo, her asthma worsened; which was nearly fatal.



This patient should not have been included in the trial. When a protocol is created for a proposed clinical trial, the investigator must employ specific inclusion and exclusion criterion. Certain groups of patients are excluded because they have certain intrinsic traits or conditions that increase their chances of serious harm from participating in the trial.

Given that the FDA has embraced the double blinded randomized placebo control trial as the gold standard for clinical research, it seems unreasonable to interpret the statement “do not harm” in a way that it would rule out the ethical permissibility of placebo control trials (PCTs). Another way to interpret the statement is that the researcher should not intentionally or purposefully harm an experimental subject. Take the experiments conducted by the Nazis as a paradigm case of this type of intentional harm. Considered in this light the statement is reasonable and normally can be satisfied by current research practices.

The researcher may not intentionally harm the experimental subject, yet there is risk involved in conducting research. Occasionally an adverse allergic reaction can lead to death. It seems that beneficence, in the sense in which the term is being employed in the Report, means do not intentionally harm the subject or put him at unnecessary risk. If it is interpreted in this sense, it seems to be applicable in principle and practice to most forms of clinical research. Further most clinical trials could meet these conditions.

### **Analysis of the Belmont Report requirement of “Justice”**

The final principle to be considered is justice. According to the Report, “Justice demands... research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.” This is often taken to mean that there should be a favorable risk-benefit ratio and that research should not be conducted exclusively on a particular group. In principle this sounds fair minded, yet in practice this concept breaks down.

Most research is conducted upon the poor and the desperate. Those with the means to pay for treatment do so, whereas those without the means to pay for treatment may enroll in clinical trials out of a desperate need to alleviate their conditions. Those who cannot afford treatment are often forced into experimental trials in hopes of a cure- one they may not receive. How the principle of justice is to be applied in practice is unclear. It sounds reasonable to argue in favor of “justice” yet I am not sure that it has a place in this discussion beyond saying that the rights of persons ought to be respected and protected.

Consider for example John Rawls’ definition of “justice as fairness”. He says that justice entails the following two conditions are met within society:

1. Each person has an equal right to the most extensive scheme of equal basic liberties compatible with a similar scheme of liberties for all.
2. Social and economic inequalities are to meet two conditions: they must be a) to the greatest expected benefit to the least advantaged b) attached to offices and positions open to all under conditions of fair equality of opportunity.<sup>188</sup>

What Rawls wants is for everyone to have the same basic scheme of rights and liberties. If there must be inequality under the law, then the inequality ought to favor the poor and disenfranchised. Under his conception of justice social and

economic inequality ought to be to the benefit the poor instead of the rich.

Inequality, say in taxes, ought to be at the expense of the rich; more money ought to be taxed from the rich and then redistributed to benefit the poor.

In the case of biomedical research, the burden of the cost as well as the benefits of such research ought to be distributed equally. Again, on Rawls' view, an unequal distribution of the benefits is only compatible with justice if it helps those "least advantaged". How could such principles be applied to clinical research?

As an application of the principle, clinical research should be conducted upon the rich and the poor. No social group should be experimented upon more than another. Further the medical interventions that are discovered by clinical research ought to be distributed equally to all members of the community. It would seem that the current practice of clinical research is unjust on Rawls' view; the spoils of clinical research are not distributed equally.

It is unjust, given Rawls' conception of justice, because the poor are more likely than the rich to participate in risky phase 1 research. The poor are less likely than the rich to benefit from new medical interventions. The only way inequality can be justified (for Rawls) is if that inequality were to the benefit of the least advantaged segment of society, (or perhaps humanity). This does not happen in practice, so the current distribution of risk and reward appears to violate his principles of justice.

There are various conceptions of the term "justice". The definition that is employed in the Belmont Report is different from the one employed by Rawls,

nevertheless, it is unclear whether the current clinical research practice is “just” under either definition. As noted earlier, the Report says, “Research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.” The reality is that the groups employed—especially in phase 1 clinical research are unlikely to be among the “beneficiaries of subsequent application of research.”

As noted in the previous chapters, for trials conducted in developing countries most of the persons employed are unlikely to receive any direct benefit. It would seem that the current research practice violates the principle of justice as stated in the Belmont Report as well as Principle 19 of the Declaration of Helsinki. Principle 19 says, “medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.”<sup>189</sup>

Does justice require that those individuals employed in the research have the potential to benefit from it? This was discussed extensively in previous chapters, but if the answer is yes, then a great deal of clinical research conducted worldwide is unjust. I am not certain that justice requires that a group of people used in research eventually receive the intervention developed in a clinical trial. Consider the following two scenarios: 1) Jim volunteers to participate in a clinical trial to develop a treatment for lupus. The data collected in the trial eventually leads to a treatment. Unfortunately Jim does not have the economic means to pay for the new treatment, and must settle for either an inferior treatment or no treatment at all.

Is this unjust? I do not think that it is. Have Jim's rights been violated because he does not have the money to buy the new medical intervention? I do not believe they have. Further, I do not think he is owed anything beyond what he originally agreed to when he entered the trial. If his participation was contingent upon him being given the eventual treatment, then a promise or contract has been broken. If he had no such clause in his agreement with the clinical researchers, then I do not see how he can demand the new intervention or claim that this situation is unjust.

If you think that he has a right to demand the medical intervention, then perhaps we should socialize the practice of medicine research. That discussion is beyond the scope of this dissertation. It would, however, provide a solution to the world medical woes. As a note: this same type of reasoning could be used to demand that farmers give away their crops to the hungry and the poor of the world, or oil companies to give away gas to drivers that need it to commute to and from work. We don't make this same demand upon them; therefore I am not sure why we should make it of pharmaceutical corporations. I will point out that capitalism is the driving force behind world commerce (and clinical research). Some have gone so far as to argue for a right to certain basic necessities like food and healthcare. It has been argued that all people, regardless of the economic means, ought to be provided with food or even healthcare by the government. I will mention this here, but the analysis of such claims is beyond the scope of this dissertation.<sup>190</sup>

Returning to the example of Jim, the experimental subject, consider a second scenario that is identical to the one described above, with one notable exception:

Jim has the economic means to pay for the treatment, but because he is of a particular ethnicity, (religion, sexual orientation, or choose your bias), the developers of the treatment decide to withhold the medical treatment from him because of their bias. I would argue that this is an injustice. A medical intervention should not be systematically excluded from any particular group, solely on the basis of any of the criteria mentioned above. It is true that economic factors dictate that large segments of humanity will not have access to medical treatment, but curing the social inequalities of the world is not the responsibility of the pharmaceutical corporations. The pharmaceutical companies and clinical researchers are not morally obligated to give medicine away. No one, not even a research subject, should have a “reasonable expectation” to have medicine handed to them for free. So long as those individuals meet the conditions I have mentioned earlier, then they should be able to justly participate in clinical research.

There is one final consideration before we leave this discussion entirely: exploitation. Perhaps the poor are not “coerced” into participating in clinical trials, but rather they are exploited by the pharmaceutical corporations and clinical researchers? I will define exploitation as follows: A exploits B when A takes unfair advantage of B. What constitutes “unfair advantage” is certainly debatable.

In this context, one can consider the vast monetary gains received by the pharmaceutical companies for the products that are developed in clinical research, and the relatively minor gain to the participants of those trials. There is a great disparity in the gains made by pharmaceutical corporations and the experimental

subjects used in their clinical trials. If the disparity is too great, then one could argue that the participants have been exploited. By this definition groups such as the poor are systematically “exploited”. What follows from this is unclear. Are all exploitative practices wrong? I argued earlier that they are not. I believe there is a threshold of exploitiveness; at some point the disparity in risk and gain is so great that, at once, a practice is exploitative and unethical. Some trials conducted in the developing world seem to breach the threshold of exploitiveness and become unethical. For example a minor disparity in the risk and benefit between participants in an agreement may be, by definition exploitative, but it is not unethical. Yet a large disparity between the risk and the gain is both exploitative and unethical.

### **Ethical Analysis of FDA Policy and Requirements**

In 1981, the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards).

In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other U.S. Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects, or "Common Rule." The main elements of the Common Rule include : 1) requirements for assuring compliance by research

institutions; 2) requirements for researchers obtaining and documenting informed consent; 3) requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping; and 4) additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children.

Both the Common Rule and the FDA regulations provide protections for human subjects in research. Almost all research conducted in the US is subject to the regulations of the Food and Drug Administration (FDA) at 21 CFR Parts 50 and 56. FDA regulations confer protections on human subjects in research when a drug, device, biologic, food additive, color additive, electronic product, or other test article subject to FDA regulation is involved. <sup>191</sup>

In my view the right of self determination is an inherent trait of competent persons. The freedom that follows from autonomy provides the foundation for a person's ability to give his informed consent to participate in clinical research. Respect for the right of self determination is a necessary condition for ethical research. The obligation to respect each person employed as an experimental subject entails certain rights for the experimental subjects and certain obligations on the part of the researchers. My defense of the concepts of personhood and the right of self determination finds its philosophical foundation in John Stuart Mill. I have argued that the right of self determination is a prima facie right of competent individuals.

Another necessary condition of ethically permissible research, in circumstances where it is possible to obtain, is informed consent. This assumes



that the person is competent to give his informed consent. It also assumes that he understands, in general terms, the nature and the risk of the clinical research that he is consenting to participate in. Taken together respect for the right of self determination (the freedom of an individual to make decisions that pertain to his life) and informed consent (in cases where the individual is mentally competent) are both necessary and together sufficient to provide for the ethical permissibility of most clinical trials.

The conditions that I have argued for are not necessarily at odds with the FDA requirements but they are more permissive in some regards. The conditions I have established are consistent with the FDA standards on many points. When considering the FDA regulations, one issue is how the FDA requirements are to be interpreted and applied to specific clinical trials. This issue will be addressed as we consider the minimum requirements established by the FDA and the roles of the institutional review board (IRB) for scientific and ethical oversight and approval of clinical studies.

### **Informed Consent**

The FDA requirements begin by stating that informed consent is an essential requirement in the protection of human subjects. Title 21 of the FDA requirements says, “No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.”<sup>192</sup> There are 14 elements listed by the FDA in order to obtain Informed Consent. Only 8 of these elements are actually required in most cases.

The following is taken out of the current federal code (21CFR50). Title 21 section 50.20 says:

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.<sup>193 194</sup>

The FDA list of requirements for informed consent seems consistent with providing an autonomous agent the information required for them to make an informed and well founded decision. Section a) 2) requires that a description of any “reasonably foreseeable risk or discomfort to the subject” be provided. In studies involving medications, there is always the potential for an adverse reaction, one that can lead to permanent disability or death.

In most cases the chances of such an event may not be very likely, but given the uncertainty involved in clinical experimentation the risk of death or disability should be disclosed. This is particularly true of studies involving novel compounds that have not been tested in humans before. Most of the recent deaths that have made headlines, such as Ellen Roche<sup>195</sup> or Jesse Gelsinger<sup>196</sup> involved phase 1 research that had never been conducted in humans. This type of study is riddled with danger and may need closer oversight and regulation. It is unclear if the experimental subjects that enroll in such trials truly understand the risk involved. In the case of Ellen Roche, an external review of the study conducted at John Hopkins found errors and omission in the study protocol and the informed consent agreement.<sup>197</sup>

Section a) 4) requires that the experimental subject be told of any alternative treatments that may be employed to alleviate his condition. I think that this is an important requirement, particularly in phase 2 or phase 3 clinical trials, where sick patients may be seeking treatment for their condition. Experimental subjects ought to be made aware of alternative therapies. Again, because of economic circumstances, some people may feel compelled to enroll in a clinical trial, just so they may have the possibility of receiving some treatment. Even a 50% chance of receiving an experimental therapy may be better than no treatment at all in the eyes of the potential experimental subject.

### **Waiver of Informed Consent**

One of the most troubling aspects, from an ethical perspective, of current federal regulations involves the waiver of the informed consent requirement. Although the federal requirements begin with a promising start, the FDA states several situations where informed consent can be waived. A few of these involve waving informed consent when endeavoring to save the patient's life. In such a situation, the patient is either incapacitated or the intervention, in the view of the physician, is the only reasonable method to save the individual's life.

Informed consent can be waived according to current FDA regulations under the following circumstances stated in Section 50.23- Exception from general requirements:

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(i) Public benefit of service programs;

(ii) procedures for obtaining benefits or services under those programs;

(iii) possible changes in or alternatives to those programs or procedures; or

(iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.<sup>198</sup>

In general, I think that waiving informed consent is unethical. I think it makes for a poor public policy. This power to waive informed consent can be abused by even the most scrupulous individuals. I have argued that informed consent is a necessary requirement of almost all ethically permissible clinical research.

Several aspects of the federal regulations raise significant ethical questions. To begin, how would it be possible that an experimental subject to be in a situation where the following condition is met, “a) 1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.” It is almost unimaginable to consider such a circumstance actually taking place. Imagine such a hypothetical case: a potential experimental subject just happens to be in a research clinic, just happens to be in a life threatening situation where he is unable to give his informed consent, and the “test article” is the only method to save his life? Such a circumstance seems rather unlikely to obtain in the real world.

Perhaps, on the other hand, the clinical researcher carries on his person samples of experimental medical interventions, just in case he runs across incapacitated person upon which to use them. Does this sound remotely feasible? How could this situation actually obtain in the real world? A clinical researcher is driving home, with a syringe filled with his newest experimental medication and happens upon a severe car accident. He finds an individual gravely injured at the scene and determines that the drug might help save his life. At this juncture,

feeling that it is the best means to save the man's life, he injects him with the compound.

There are several problems with the above situation. To begin, this is not even an example of clinical research. Further, how can an experimental therapy or intervention be the best or only means to save an individual's life? This clause of the federal code is troubling for several reasons. One of the most important is the fact that it has been used to justify employing experimental interventions in emergency settings. This entire clause of the FDA code is unethical and should be removed. If this entails limiting or restricting clinical research within an emergency setting then so be it. Just because someone is incapacitated or on their death bed it does not follow that physicians have *carte blanche* to experiment upon them! Trying a new treatment, in the absence of a standard treatment, is one thing systematically experimenting upon ER patients is another.

If anything the researcher is trying to provide care for the patient not clinical research. I do not see any reason, in such an outlandish set of circumstances, for the researcher to employ an experimental therapy, one that has not been approved for use. One of the only situations where I could imagine this regulation being employed would be emergency care research. Nevertheless, I deny that such trials are ethical. There seem to be alternative settings, where informed consent could be obtained, in which these interventions could be tested. If this is the case, then interventions should not be tested in a setting where informed consent cannot be obtained.

Consider, once again, the Polyheme trial mentioned in the introduction. In this trial, which was developed to test the efficacy of an artificial blood substitute known as Polyheme, the substance was used at 32 trauma centers across the US. The patients were given Polyheme on the accident scene and at the trauma center. In my view, this still does not constitute a legitimate circumstance to invoke this clause. The principle says the human subject is in a life threatening situation necessitating the use of the test article. If the ambulance is stocked with normal human blood, then there is no reason to use artificial blood. In a normal circumstance the paramedics will use saline solution to treat victims. It is unlikely to imagine a scenario where society has run out of salt water.

The makers of Polyheme, Northfield laboratories, claim on their website that, “The trial was conducted using an exception from the requirement for informed consent requirements under 21 CFR. 50.24. This provision is granted when patients are in a life-threatening situation requiring emergency medical intervention, available treatments are unsatisfactory, previous studies demonstrate the potential to provide a direct benefit (in the form of increased survival) to enrolled patients, the risks are reasonable in relation to what is known about the patients’ medical condition, the risks and benefits of standard therapy, and the risks and benefits of the proposed intervention. It is expected that patients enrolled in this trial will be unable to provide informed consent because the nature and extent of their injuries.”<sup>199</sup>



The code in question, cited to justify what is, in my view clearly unethical research is stated as follows:

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;  
(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and  
(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;  
(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and  
(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.<sup>200</sup>

Regardless of what the federal code states, this type of research violates the rights of individuals and is ethically impermissible. Even if we were to accept the

ethical permissibility of the clauses found in the federal code many of these conditions were not met by the Polyheme clinical trial. The first condition, (1) states that “available treatments are unproven or unsatisfactory”; this condition was violated in this trial. It is clearly false to say that there is no proven alternative therapy. There is a proven, time tested treatment: Real Blood! Standard protocol for accident victims is to give them a saline solution until their blood type can be matched and confirmed.

It is true that times when there is a scarcity of blood, but in the United States such shortages are a rarity. Further an investigation by ABC News found that another condition was systematically violated in the trial. Condition (2) subsection (i) says, “The subjects will not be able to give their informed consent as a result of their medical condition” yet in many cases Polyheme was given to accident victims with relatively minor injuries that were competent to give their informed consent. In cases where potential test subjects were awake, aware, and competent, they were still given the blood substitute without their knowledge or consent.<sup>201</sup>

A further consideration is this: in early trials, experimental subjects suffered severe adverse reactions to artificial blood. This experimental trial represented a serious risk to the subjects involved. According to confidential documents from Northfield laboratories, obtained by ABC News and shown on the news program 20/20, “show that a previous Polyheme experiment had to be stopped because of safety issues - 10 of the patients had heart attacks and 2 died.”<sup>202</sup>

I find it amazing that with the amount of government regulation and oversight that this trial could be approved and conducted in the United States. The fact that this trial happened at all raises several questions. One question has to do with how the rules and regulation are to be interpreted and applied. This is a problem that was noted in the discussion of both the Nuremberg Code and the Declaration of Helsinki. In the US that job of interpreting the laws and regulations falls on the shoulders of ethics review boards. Determining the relevance and applying these principles to the practice of clinical research has fallen upon the Institutional Review Board (IRB) system in the United States.

### **The IRB System and Ethical Oversight**

Under the current research structure an institutional review board (IRB) evaluates most research proposals involving human subjects. This committee is a group of experts that considers the scientific validity of the research and the ethical permissibility of such research. The IRB system is not without its flaws. The rationale behind the IRB system is that an independent entity is best qualified to judge the ethical permissibility of clinical research. It is argued that researchers may be biased or overlook potential risk to the research participants. Given this possibility, having a group of individuals who have nothing directly at stake in the project review it seems reasonable. By appointing an independent entity with no stake in the research, the danger of bias is, in theory, avoided.

The FDA defines the role and composition of the IRB as follows:

Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its

members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.<sup>203</sup>

Although I have previously argued against the use of an external review board in principle, (and I do not feel that it is a necessary requirement of ethically permissible research) in practice I am not completely against the idea. I think that the IRB ought to limit its considerations to the methodological and scientific questions involved in research. If the IRB can vouch of the scientific validity of the research, and the understandability of the informed consent agreement (ICF) then the individual experimental subject can be trusted to determine for themselves if he or she wants to participate in the research.

This assumes, of course, that the subject's consent is requested. I think that the vast majority of clinical trials that are conducted without obtaining informed consent are unethical. If the risk involved is so great that most individuals will not consent to participate, then scientist and physicians are going to have to explore other ways to confirm the efficacy of an intervention. If there are no other means, then certain questions will have to be left unresolved.

Another issue raised concerning IRBs is how they interpret and apply the applicable federal regulations. Empirical data has been collected regarding how various IRBs evaluate the methodological and ethical considerations of clinical trials.<sup>204</sup> There have been several cases where trials that were not epistemically sound were approved. Given that the IRB is supposed to contain experts in clinical research, this should not happen. The fact that a research protocol is

created by clinical researchers ought to rule out the possibility that it contains epistemological defects. One would think that they would know how to create a scientifically valid research study, but occasionally they do not. Given the risk involved in clinical research, oversight to assure sound methodological considerations appears to be a good idea.

IRBs are not uniform in their training or composition. They do not evaluate protocols of clinical research in the same way. In fact they may not evaluate the nature of benefit and risk in a uniform manner either. In an example below I examine a phase 1 trial involving patients with Alzheimer's disease. The trial was initially rejected by one IRB and then approved by another. After further discussion (and expert ethical analysis) the study was then reviewed by another IRB and unanimously approved. In defense of the second IRB's decision, they were provided with further evidence on the issues involved in the study.

The fact that different IRBs arrive at various divergent decisions regarding the methodological soundness and ethical permissibility of clinical research appears to call into question the legitimacy of the entire IRB review system. Some IRBs are more liberal with their interpretation of the ethical standards than others. This has led to a practice known as "IRB shopping". Certain IRBs acquire a reputation for being liberal in their approval practices. This leads pharmaceutical corporations to send their protocols, which may have been previously been rejected, to them. It is not uncommon for a rejected clinical trial protocol to travel from one IRB to another. When applying for IRB approval the FDA requires that

the IRB be informed of previous reviews of the clinical trial. In practice sometimes this condition is met, at other times it is not.

In the end, the IRB system has added another level of review and bureaucracy to the approval process for medical interventions, but it is unclear where it has rectified many of the issues for which it was originally created. As I have argued earlier, I think that oversight cannot hurt, so long as it does not infringe upon the rights of potential experimental subjects to participate in clinical trials of their choosing- so long as those trials have scientific validity and address important medical questions.

### **Phases of Drug Trials**

The FDA has several levels, or phases of trials. These phases will be considered, because the nature of the subjects involved (specifically well or sick, young or old, mental competence) change, in morally significant ways, depending upon the phase of the clinical trial. Under the current structure of regulations that has been adopted and endorsed by the FDA, most patients in clinical trials involved in clinical research ought to understand that they are receiving no direct benefit from their participation in a study.

The FDA requires 3 to 4 phases of study before a drug is approved to go to market. Each of these phases of study raises specific ethical questions in part because they employ diverse methodologies and specific types of experimental subjects. Phase 1 studies normally enroll healthy volunteers, whereas phase 2 and 3 studies are usually conducted on sick patients that have the disease for which the intervention being tested is targeted.

**TABLE 5.1 - Phases of Drug Studies**

<b>Phase I:</b> Researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
<b>Phase II:</b> The study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
<b>Phase III:</b> The study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will ensure safe usage.
<b>Phase IV:</b> These studies are done after the drug or treatment has been marketed. The testing continues to collect information about the effect of the drug or treatment in various populations (such as children) and determine any side effects from long-term use.

Clinical trials are conducted in a myriad of settings including doctor's offices, hospitals, and research centers around the country. The settings themselves may be ethically significant because many doctors recruit test subjects from a pool of their own patients. This may lead to a violation of the physician's therapeutic obligation, allow him to exploit his relationship with his patients, or unduly influence his patients into participating in clinical research.

Again this has been discussed in early chapters. This is an inherent danger found in the current practice of clinical research. One way to resolve this issue is to restrict clinical trials to specific settings, such as centers devoted entirely to conducting clinical trials. If this were the case, then physicians would not be experimenting upon their patients. There are a number of research centers devoted entirely to conducting clinical trials. Such research centers are normally used for phase 1 studies, but they could be expanded to other phases of clinical research.

Normally, an experimental drug is tested in a test tube or in animals before being used on humans. This is known as the Pre-Clinical Phase of research. If the

drug appears to be safe, and possibly effective in animals, the company will then provide this information to the FDA, requesting approval to begin testing the experimental drug in humans. The FDA estimates that only about 0.1% (or one in one thousand) compounds developed in laboratories pass pre-clinical trials and advance to FDA-regulated clinical trials.<sup>205</sup>

Phase 1 trials are used to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects. Usually, a small number of healthy volunteers (between 20 and 80) are used in Phase 1 trials. Phase 2 trials include more participants (about 100-300) who have the disease or condition that the product potentially could treat. In Phase 2 trials, researchers seek to gather further safety data and preliminary evidence of the drug's beneficial effects (efficacy), and they develop and refine research methods for future trials with this drug. If the Phase 2 trials indicate that the drug may be effective--and the risks are considered acceptable, given the observed efficacy and the severity of the disease--the drug moves to phase 3 studies. In Phase 3 trials, the drug is studied in a larger number of people with the disease (approximately 1,000-3,000). This phase further tests the product's effectiveness, monitors side effects, and, in some cases, compares the product's effects to a standard treatment, if one is already available. As more and more participants are tested over longer periods of time, the less common side effects are more likely to be revealed.

Phase 2 and Phase 3 clinical trials generally involve a "control" standard. In many studies, one group of volunteers will be given an experimental or "test" drug or treatment, while the control group is given either a standard treatment for



the illness or an inactive pill, liquid or powder that has no treatment value (placebo). This control group provides a basis for comparison for assessing effects of the test treatment. In some studies, the control group will receive a placebo instead of an active drug or treatment. In other cases, it is considered unethical to use placebos, particularly if an effective treatment is available. Withholding treatment (even for a short time) would subject research participants to unreasonable risks. Sometimes, Phase 4 trials are conducted after a product is already approved and on the market to find out more about the treatment's long-term risks, benefits, and optimal use, or to test the product in different populations of people, such as children.

### **Ethical Analysis of Phase 1 Clinical Trials**

In phase 1 trials researchers test an experimental drug or treatment in a small group of people (20-100 [usually] healthy volunteers, but can include sick patients) for the first time to determine the metabolism and pharmacologic actions of these drugs, their side effects associated with increasing doses, and any early evidence of effectiveness.<sup>206 207</sup> In the phase 1 trials healthy volunteers are recruited to study the pharmacodynamics and pharmacokinetics of the drug in humans. Most test subjects enrolled in clinical trials of this type understand that they are not going to receive any direct benefit from their participation in a study.

In phase 1 clinical trials the majority of test subjects consent to experimentation because they are compensated financially. Prima facie, these subjects stand no chance of direct benefit from such research, and do stand a probability of being harmed- perhaps severely. These experimental subjects seem

to violate the regulations that require a favorable risk benefit ratio. If such a favorable risk-benefit ratio is required for ethically permissible research, then this research is unethical. I have argued that such a ratio is not required.

I have argued that competent persons are at liberty to enroll in experimental research, even if it carries a high or unknown risk. These subjects spend their time in a clinical setting, receive treatments which will be of no direct benefit to them, and risk deadly side effects all for money. If you are willing to sign an informed consent agreement that states, “Any drug can, very rarely, cause allergic reactions that can be fatal”<sup>208</sup> for the sole purpose of financial gain, then I will argue that this is your right based upon a conception of the right of self determination.

The notion of the right of self determination of the person entails the right to make decisions, including the choice to participate in a clinical trial. The fact that people do in fact participate in these studies does raise significant questions. As has been discussed already, it may be the case that, the poor, or the uneducated can be compelled, by the need for money or the lack of understanding, to participate in a clinical study for which most people of means would not consent. For some of these individuals participating in clinical research is a full time vocation. They participate in numerous trials each year to make a living. One could reasonably argue that it has developed into a form of work.

This supports the analogy mentioned in previous chapters. I have argued that enrolling in clinical trials, particularly those where there is no direct benefit beyond financial compensation, is analogous to work. In support of this thesis is

the fact that many of us are compelled to take jobs that, all things being equal, we would rather not.

This view is at odds with the FDA position. According to the FDA, “The IRB should review the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present an undue influence.”<sup>209</sup>

<sup>210</sup>Again, I have argued that coercion in most cases involves a threat of some kind. This condition is not met when persons volunteer and are then paid for their participation in clinical trials. Payment may serve as an experimental subject’s primary motivation for enrolling in the trial, but I do not find this to be ethically objectionable.

The FDA says that a bonus may be paid to subjects for completing a study. “A bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.” I think that what the FDA has in mind is that subjects should not feel compelled to cover up side effects or remain in a clinical trial, where they would otherwise withdraw, because of financial incentives. The reality however is that most of these subjects would not be participating in the clinical research, unless there was a financial incentive. In chapter 2, I attacked the coherence of “undue influence”. It seems as though most test subjects would not enroll in research for which they had no prospect of direct benefit unless the financial compensation were sufficient to “influence” them into participation.

Martin Wilkinson and Andrew Moore have argued for financial compensation of experimental subjects.<sup>211</sup> Here is how they frame the question of payment.

“Some researchers would find it worthwhile to pay inducements in order to attract enough subjects. Those who would accept this reward would not do so unless it was worth it to them. As a result of offering the reward, the researchers get the subjects they want. As a result of participating, the subjects get the reward they want. Both are better off. No one is worse off. Inducement is thus a good thing.”<sup>212</sup> Wilkinson and Moore note some of the arguments against inducement claim that “consent is invalidated by inducement.”<sup>213 214</sup> Yet, as they note, many people perform tasks, under deplorable conditions, for money. “There is no suggestion in the vast majority of cases that their being paid undermines the voluntary nature of their actions.”<sup>215</sup> I find payment to experimental subject no more objectionable than employing people to perform jobs that I, myself, would not take. Is a crab fisherman “coerced” because he is paid a percentage of the catch? Statistically, it is one of the most dangerous jobs in the world, yet by the same token it can be one of the highest paid. No doubt the adventurous crab fisherman in the Bering Strait may be influenced to take the job primarily because of the money. Yet I do not see how this leads to a coercive circumstance.

On the other hand, if, while on a trip to Alaska, I am kidnapped and taken aboard a fishing boat and forced to work, then I would say that this is an example of coercion. If I am given the choice by my abductors to work or be thrown overboard, then I would rightly say I have been coerced into working on the boat. Given the two cases, one where I volunteer to serve on the boat and the other where I am forced to do so, which is more analogous to the case of clinical research? I maintain that the case of voluntary consent is analogous to most

research trials. In a case where an experimental subject has given his voluntary informed consent he has not been coerced. Coercion, as argued previously, involves a threat of harm or force on the part of the coercer. Normally, this is not the case in clinical trials.

I think that informed consent can answer many ethical questions, but in some instances, it raises many more questions and concerns. Why would someone consent to participate in a potentially life threatening clinical trial? The reality is that people engage in all sorts of dangerous activities on a regular basis. Reality shows, such as Jack Ass or Holy #\$@!, showcase the actions of imbeciles engaged in all manner of stupidity. In my view, it is their right to ride mountain bikes off of cliffs, wrestle with polar bears, or enroll in clinical trials.

Informed consent goes a long way towards resolving many of the ethical objections raised to clinical research. Although informed consent can answer many of the ethical objections raised to clinical trials it does not mitigate the duty of the clinical researcher to protect the research subject from undue harm. It provides a basis for the ethical permissibility of all phases of clinical research and of all experimental methodologies including Randomized Control Trials (RCTs) and double blinded placebo control trials (PCTs).

### **Case Study: Phase 1 Alzheimer Study**

There have been several clinical trials conducted since the Belmont Report that seem to violate the ethical principles contained in the document. In some cases patients are not competent to consent to participate in research; in other cases informed consent was not sought. Is it ethical to experiment upon individuals that

cannot consent? The literal reading of the Nuremberg Code seems to prohibit such studies; the current version of the Declaration of Helsinki allows it. The FDA permits research of this type as well. I think that some of these studies violate the principles I have established as the minimum necessary requirements for ethically permissible research. The study to be considered does not violate the principles that I have defended.

Recently an IRB reviewed a proposed protocol for a clinical trial involving a new medication for the treatment of dementia. This study was for a phase 1, “first in man”, trial. Most studies of this type are performed in healthy volunteers. These trials are conducted to test the tolerability and pharmacodynamics response of a medication within human physiology. Since these compounds have never been tested in vivo there is no firm foundation with which to judge the response the compound may produce within a human being. Many of the recent, high profile, deaths that have taken place in clinical trials occurred in phase 1 clinical research. Although such trials are normally conducted in healthy volunteers, this study was different in that the researchers wanted to test the new compound in patients’ afflicted with Alzheimer’s disease. This study raised a number of ethical and epistemic issues. Should drugs or medical interventions, in general, be tested on healthy or sick patients in phase 1 studies?

The ethical norm that has been endorsed by the FDA and other regulatory organizations is that phase 1 trials should normally be conducted in healthy volunteers. It has been argued that sick patients are in a “vulnerable position” because of their illness and should not be asked to participate in phase 1 trials.

I disagree with the “ethical norm” that drugs ought to be tested on “less vulnerable” populations than more vulnerable. First of all, it is not clear that just because persons are sick that their judgment is compromised or they are prima facie in a vulnerable position. I think that by employing people with the disease in the first phase of research, an entire step in the research process can be eliminated. Ethically, I think that the fact that fewer test subjects will be put at risk, justifies testing on subjects that are ill as opposed to beginning testing of medical interventions on healthy patients. Again, I think that this can be justified because an entire round of testing can be eliminated and fewer subjects will be put at risk.

Further, there is the possibility that the subjects will benefit directly by being participants in this study. I think that it is much more difficult to justify giving drugs to healthy volunteers, given that their only motivation to participate in the study may be money. The poor and the uneducated are often compelled to participating in such studies because of economic need. Even if the study participants will not benefit directly for participating in this trial, the trial itself may lead to generalizable knowledge about their condition which in turn may benefit them or others like them in the future.

Another issue to be considered has to do with scientific reliability. Epistemically, testing a drug on a healthy patient might result in misleading data. It could certainly be the case that a drug has no side effect in healthy volunteers but has severe side effects in ill patients. Ultimately the only way to know the consequences of employing a drug or medical intervention is by administering it to the target population of individuals with the disease.

This trial involved another important consideration: the ability of a patient with dementia to give consent. This trial was limited to patients with mild to moderate dementia. Are patients with mild to moderate dementia competent to give informed consent? According to the Alzheimer's Association, patients with mild dementia can give informed consent. They also maintain that it would be a violation of the principle of justice to outright exclude the entire class of patients with dementia from clinical testing.

Several clinical trials have been conducted upon subjects that cannot give informed consent. In 1997 the New England Journal of Medicine published the following study involving patients diagnosed with moderate to severe dementia: "A Controlled Trial of Selegiline, Alpha-Tocopherol, or Both as Treatment for Alzheimer's disease."<sup>216</sup> There are numerous other studies that I could cite, but in general, patients with cognitive impairment are not, as a rule, excluded from clinical trials. In this particular study, I would argue that consent should be acquired from both the patient (if possible) and an authorized legal representative.

### **Ethical Analysis of Phase 2/3 Clinical Trials**

In a phase 2 clinical trial the experimental drug or treatment is given to a larger group of people (100-300) to see if it is effective, further evaluate its safety, and to determine the common short-term side effects and risks. In this phase of research sick patients are recruited as volunteers. The experimental drug must show a unique benefit and/or a unique safety benefit profile. Dramatic remissions or recoveries in treated patients need to be demonstrated. Minimal benefits may be significant finding for previously untreatable diseases where there is no current



standard of care. This phase could last up to two years, and about 50% of the drugs that enter this phase complete it successfully.<sup>217</sup>

Phase 3 studies are used to confirm the efficacy of a medical intervention. In this phase of research sick patients are recruited as volunteers as well. Results from the studies will provide the necessary data for the FDA to make its final decision, as well as supply the data for physician labeling. Expanded, controlled, and uncontrolled trials are performed with large groups of people (several hundred to several thousand) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, collect information that will allow the experimental drug or treatment to be used safely, and to evaluate the overall benefit-risk relationship of the drug or treatment. In general, the studies last for 1 to 3 years. 70-90% of the drugs that reach this phase complete it successfully.<sup>218</sup>

As noted above, these two phases of research involve experimenting upon sick patients. In this case the patient must be informed about the experimental nature of the research, and the fact that he may not benefit directly from the research. As has been discussed in previous chapters, many experimental subjects are under the false impression that there is a guaranteed therapeutic benefit from participating in a clinical trial. In most cases, this will not be the case. This idea is known as the therapeutic misconception. It is true, however, that patients enrolled in phase 2 and phase 3 research stand the chance of benefiting eventually from the research if the treatment is effective for their condition.

One definition of the therapeutic misconception is stated by Paul Appelbaum as follows: A therapeutic misconception occurs when a subject transfers to the

research setting the presumption that obtains in ordinary clinical treatment: that the physician will always act only with the patient's best interest in mind.<sup>219</sup> The therapeutic misconception occurs when the test subject believes that his participation in a clinical trial will lead to a direct benefit for his condition. In most cases, there is no guarantee of direct benefit. As I have argued earlier I think that the therapeutic misconception raises questions about the quality of informed consent. If informed consent is properly obtained, and the research involves no direct benefit, then the subject should not suffer from the therapeutic misconception.

#### **Ethical Analysis of Phase 4 Clinical Trials**

Post-marketing studies to define additional information including the drug's risks, benefits, and optimal use. After a successful completion of Phase 1-3 testing, a company will submit the results of all of the studies to the FDA to obtain a New Drug Application (NDA). Once the FDA grants a company with a NDA, the company can market the drug to the public. The approval review could take up to one year.<sup>220</sup> Phase 4 studies are performed on drugs already approved for market. The testing continues to collect information about the effect of the drug or treatment in various populations (such as children) and determine any side effects from long-term use.

Because these studies are often conducted on pediatric populations they raise significant ethical questions. Should children be employed in clinical research? The FDA has special requirements for such research. It is argued that children cannot give their consent because they are not old enough to understand the

dangers involved in clinical trials. In place of consent, the term assent is often employed within the literature to denote consent obtained from a child. This usually goes hand in hand with consent being obtained from a family member or legal representative. The term is most prevalent in research involving children.

The FDA has several provisions related to pediatric research:

The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.<sup>221</sup>

The FDA supports the thesis that clinical research upon pediatric populations is ethically permissible so long as the parents give their consent and if the child is of age they “assent” to the experiment. The term assent is often used in reference to persons that are not able to give informed consent to clinical research. It means that they agree with being employed in the experiment, even if they do not understand what this entails.

Prima facie the term assent might seem either superfluous or vacuous. I think that the rationale behind getting the subject’s consent is that you would not want to drag the child kicking and screaming into a research experiment. A child should be a willing participant in the clinical study. I think that the ethical permissibility of trials conducted upon subjects that cannot consent varies depending upon several factors. The factors that have bearing upon the ethical permissibility of such trials include: the potential risk and benefit to the experimental subject, the severity of the subject’s condition, and the importance

or value of the knowledge gained by the clinical research. I think that populations that cannot consent are in fact “vulnerable”.

I think that such research should be restricted. The following conditions should be met in order for such research to be ethically permissible:

- 1) Informed consent must be obtained by the guardian of the test subject.
- 2) The research must be directly related to a condition the test subject suffers from.
- 3) Where there is an accepted standard therapy, the trial must not contain a placebo control.
- 4) The research should not be life threatening or contain the reasonable likelihood of serious harm or injury.

Although the current federal standards seem to contain many of these requirements, how they are employed, in practice, is troubling. I think the research should only be conducted if the population stands the chance of direct benefit from the trial. In other words, they should have a condition that could, potentially, be alleviated from their participation in the research. Further, I think the use of a placebo is unjustified if there is an accepted standard treatment. Trials in these cases should only be comparative studies of different medical interventions. This type of trial is known as an active control trial, (ACT). I don't think it is justifiable to make a child suffer receiving a placebo if there is a standard therapy.

## **Conclusion**

In this chapter I have considered the ethical foundations of FDA requirements for clinical research. The importance of these regulations cannot be overstated, because they are employed around the world to conduct clinical research. Even the best standards will not stop unethical clinical research if they are not consistently applied. In the last fifty years the rights of patients and experimental subjects have been expanded. There are many more protections in place now than ever before. In other words, progress has been made.

And yet, even with all the progress that has been made, trials are conducted every day that violate these principles. The answer to these problems is vigilance. In principle I think any competent person may consent to participate in a clinical trial, but in practice I think many of these experimental subjects do not understand the inherent risk involved in clinical research. Another consideration in this discussion is money. No one should be so naive as to assume that pharmaceutical corporations have altruistic motives when they conduct research overseas in developing countries. Often trials are conducted in these locations because it is easier to recruit experimental subjects, subject them to interventions that no one in the West would be willing to undergo, and because it is easier to bend or break the rules in other jurisdictions.

Last summer I attended an international conference on clinical research. Many of the researchers complained that the IRB system slowed the process of clinical research. One woman, a doctor and researcher, said she had solved this problem at her institution by being on the IRB. Because she was on the IRB she could get

her research proposal approved in a timely manner. She had no conception of an inherent conflict of interest, nor did she seem to understand that IRBs are supposed to be independent review entities. All the regulations in the world will not stop unethical research if they are not understood or applied in practice.

Again I have defended several requirements, the most important of which is informed consent. In my view the right of self determination is inherent in each person and the freedom this entails provides the foundation for our ability to give informed consent to participate in clinical research. Respect for the right of self determination is a necessary condition for ethical research. The right of self determination entails certain rights for the research subject and certain obligations for the researcher. It is more robust than what is often termed “respect” found in the literature. Another necessary condition (in circumstances where it is possible to obtain) is informed consent. This assumes that the person is competent to give their informed consent. It also assumes that he or she understands, in general terms, the nature and the risk involved in the clinical trial. Taken together the right of self determination and informed consent (in most cases) are necessary and sufficient in normal circumstances for scientifically valid clinical research to be ethically permissible. If these principles were applied, then the vast majority of clinical research would be able to accomplish the task of scientific progress while at the same time honoring respect for human dignity.

## APPENDIX 1

### The Hippocratic Oath (Ancient)

I swear by Apollo Physician and Asclepius and Hygieia and Panacea and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath and this covenant:

To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art - if they desire to learn it - without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but no one else.

I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.

I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.

Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.

What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself, holding such things shameful to be spoken about.

If I fulfill this oath and do not violate it, may it be granted to me to enjoy life and art, being honored with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.

*Translation from the Greek by Ludwig Edelstein. From The Hippocratic Oath: Text, Translation, and Interpretation, by Ludwig Edelstein. Baltimore: Johns Hopkins Press, 1943.*

## **APPENDIX 2**

### **The Hippocratic Oath ( Modern)**

I swear to fulfill, to the best of my ability and judgment, this covenant:

I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.

I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.

I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.

I will prevent disease whenever I can, for prevention is preferable to cure.

I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

*Written in 1964 by Louis Lasagna, Academic Dean of the School of Medicine at Tufts University, and used in many medical schools today.*



### APPENDIX 3

#### The Nuremberg Code

1. 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, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements 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. 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.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

## **APPENDIX 4**

### **The World Medical Association Declaration of Helsinki**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the  
29th WMA General Assembly, Tokyo, Japan, October 1975  
35th WMA General Assembly, Venice, Italy, October 1983  
41st WMA General Assembly, Hong Kong, September 1989  
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996  
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000  
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002  
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

#### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

#### B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH  
COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

**Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven

therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

**Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.



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