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Clinical trial informed consent: Outsiders and the love-justice correlation

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CLINICAL TRIAL INFORMED CONSENT:
OUTSIDERS AND THE LOVE-JUSTICE CORRELATION

by

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Abstract

Clinical trial informed consent is one of the most pressing issues of research ethics. As the Western world moves toward a harmonization of clinical research practices, scholars and clinical researchers have begun to discuss methods that can adequately assure a more valid clinical research informed consent process.

One resource for insight and guidance on the issue of clinical trial informed consent is the theologically trained medical ethicist. Because of the theological and philosophical explications on love and justice that are emphasized in their training, such individuals are uniquely qualified to address the institutional and individual parameters inherent in the clinical trial informed consent process. These parameters are grounded in the clinical trial informed consent paradigm categories of recruitment of potential subjects, the "stranger" or "outsider" status of the potential subject, and the notion of clinical trials as endeavors of human experimentation. The argument for a unique qualification in this field relies upon the affinity found between these component categories of the clinical trial informed consent paradigm and the love and justice explications of Paul Ramsey and John Rawls. Specifically, these explications are concerned with the notions of care
for the stranger and justice in institutional structures.
Acknowledgements

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CHAPTER ONE

INTRODUCTION

Introduction and statement of the thesis

The thesis of this dissertation is that the theologically trained medical ethicist is uniquely qualified to inform a discussion on clinical trial informed consent. The strength of this claim rests upon the correlation present between the notions of love and justice and the component paradigm categories of clinical trial informed consent. Reflection on the structure and function of this paradigm, the understanding of love and justice as presented in the curriculum of the theologically trained medical ethicist, and the explications of others validates this assertion.

At the outset, I have chosen not to approach this topic with what Langdon Gilkey, in describing techniques and procedures, might refer to as the "driving school" method of analysis, i.e., what clinical trial informed consent should be, what it is in practice, and how the theologically trained medical ethicist might help remedy identifiable deficiencies. Although there are elements of this methodology present--I do address all of these issues--the
central theme of the dissertation is less strictly procedural and more reflective of the basic hypothesis that clinical trial informed consent and the theologically trained medical ethicist have business together. Nor is this dissertation, despite its claimed significance and applicability to theological training in health care ethics, itself purely a theological analysis. For example, while there is a strong linkage between the notion of love and theological thought, the dissertation's argument does not depend upon any necessarily theological significance of the notion of justice. Rather, the argument is both curricular and theological. Because of the correlation present between the very essence of clinical trial informed consent and the notions of love and justice, the curriculum of the theologically trained medical ethicist, with its theological and philosophical explications on love and justice, provides such individuals with a unique qualification to address the situation at hand.

For example, one of the major sources for my analysis is John Rawls, a secular philosopher. One would be hard pressed to attempt a theological analysis that relies upon a Rawlsian construct, and no such attempt will be made in this study. Rawls' familiarity and potential usefulness to the theologically trained medical ethicist are not dependent upon any theological significance of his work. However, the
theologically trained medical ethicist is well-schooled in Rawls' "justice as fairness" theory—a theory often invoked, either in defense or in rebuttal, in supporting his or her own claims. In fact, theologically trained ethicists, when arguing either with or in opposition to a Rawlsian perspective, are quite frequently indistinguishable from their secularly-trained philosopher colleagues.²

Rawls' familiarity to the theologically trained medical ethicist is not a sufficient framework on which to build an analytical and prescriptive argument on clinical trial informed consent. Rawls' applicability to such an issue is limited to the notion of institutional forces at work in the realm of clinical trial informed consent, which I will refer to as the institutional element of informed consent, and the relationship between these forces and structures and his theory of the "basic structure" of society. One must also be mindful of the fact that clinical trials are conducted on human subjects, and further that these subjects are actually "outsiders" or "strangers" to the medical research system. In service of this aspect of the clinical trial informed consent paradigm, which may be viewed as the individual element, I shall call upon the thought of Paul Ramsey, who has suggested, via his distinctively Christian deontological stance, that one has an obligation to address the needs of one's neighbor.³
It is not the goal of this dissertation merely to "apply" the thought of Ramsey and Rawls, or even the notions of love and justice, to the realities and problems of clinical trial informed consent. Although such application has much practical significance, and will indeed be explored, the validity of the dissertation's claims does not rest upon any such application, even if successful. Rather, I argue that there is an affinity, or correlation, between love and justice, as formulated by these two thinkers, and the component categories that constitute the paradigm of clinical trial informed consent. It is this correlative relationship that validates the claim of a unique qualification for the theologically trained medical ethicist who attempts to deal with the important and timely issues of informed consent in clinical trials.

A critical priority of this dissertation is the existence and acceptance of clinical trial informed consent as a fundamentally different paradigm from informed consent for medical treatment. The existence of this separate paradigm is reflected in three distinct categorical differences between these two models of informed consent. These differences are not only definitional, but also point to potential problems in the implementation of informed consent for clinical trials.
First, clinical trial informed consent is part of a recruitment process—a process that begins whenever the potential subject is first made aware, or in any way first becomes aware, of the clinical trial. Because clinical investigators are often under intense pressure, either real or imagined, to recruit subjects for trials for which they have a responsibility, there is a discernible potential for coercion or undue persuasion of potential research subjects. In clinical trials, unlike the treatment scenario, these potential subjects are approached by the physician-investigator, either individually or via advertising, and asked if they are interested in participating in the research project.

Second, persons being recruited for clinical trials are frequently outside the medical environment. That is, such individuals are oftentimes not patients in the same medical system in which the research is to be carried out. In fact, in many cases potential clinical trial subjects are not patients at all. They possess no other health care system status than possibly satisfying the trial’s inclusion and exclusion criteria. Unlike patients, potential clinical trial subjects often enter the informed consent negotiation with no "medical identity." Thus potential clinical trial subjects may be viewed as "outsiders" or "strangers" by
investigators—a relationship that is, of course, potentially reciprocal.

Third, and quite possibly most important, clinical trial informed consent is in reality consent to participate in a human experimentation project. The basic purpose of most clinical trials is, after all, to determine the efficacy and safety of an unproven pharmaceutical compound. More important than the experimental status of the agent to be tested, however, is the fact that clinical research is conducted under extremely rigid protocols, or plans of study, that prevent individualized therapy for given subjects. Thus, unlike patients in the medical treatment scheme, clinical trial subjects do not participate in a therapeutic alliance with the physician.

The paradigm of clinical trial informed consent is significant, as it points to the utilization of the informed consent process for the recruitment of outsiders into the realm of human experimentation. In this regard, clinical trial informed consent is not merely a variation of informed consent for treatment, but rather represents a fundamentally distinct process. The two models, while similar in regard to the ethical priority of respect for persons, are strikingly different in the manner in which they are utilized in actual practice.
The suggestion that clinical trial informed consent represents a fundamentally distinct paradigm invites an examination of potential barriers to its implementation, as well as suggestions for more valid informed consent processes. Documentation of the uniqueness of clinical trial informed consent does little in the way of determining its suitability as an instrument for the recruitment of outsiders into the realm of human experimentation. Valid informed consent in the clinical trial scenario is not a given. There is no "unseen hand" that works to correct inequities and other abuses in the system. Toward this end, the dissertation will be concerned with the limitations of clinical trial informed consent as paradigm. These limitations may be found within each of the three component categories of the paradigm, i.e., recruitment, the notion of outsider, and human experimentation. For example, the recruitment of potential clinical trial subjects does not occur as an isolated interchange between equal human beings, but rather within a complex matrix of institutional forces and policies—contingencies that may negatively influence the fairness of the process. Also, the outsider or stranger status of the potential subject may invite distancing in the relationship between that individual and the investigator conducting the trial—a distancing that discourages meaningful dialogue between the two parties. Further, the fact that clinical trials are actually projects of human
experimentation is often not fully appreciated by either the investigator or potential subject. This attitude may easily compromise the ethical validity of the clinical trial informed consent process, since one of the fundamental tenets of research informed consent is that the potential subject be informed of the exact nature and purpose of the project.  

The limitations of clinical trial informed consent may be addressed in many ways. Legislation may be enacted requiring stringent procedures for the informed consent transaction. Institutional review boards, in addition to prospectively approving the research protocol and consent form, might take a more active role in insuring the ethical integrity of the entire clinical trial informed consent process itself. Curricular reforms in medical education could introduce the priority of informed consent as ethical process. Further, constructive guidance may be sought from health care ethicists, philosophers, and other scholars and practitioners.

To validate the claim that the theologically trained medical ethicist is uniquely qualified to address the issue of informed consent in clinical trials, this dissertation will argue that the notions of love and justice, as explicated in the respective thought of Paul Ramsey and John Rawls, are useful resources for insight into effecting
valid informed consent in the clinical trial scenario. Specifically, I will argue that the first two component categories of the clinical trial informed consent paradigm, i.e., potential subject recruitment and the notion of outsider, are fundamentally correlative with the notions of justice and love as explicated in the respective thought of Rawls and Ramsey. Further, I will suggest that the third component paradigm category, i.e., the human experimentation element of clinical trials, demands that corrective action be initiated toward the deficiencies in the clinical trial informed consent process.

A major challenge to the theologically trained medical ethicist is to offer guidance and insight that are not only intelligible to a pluralist world, but are also acceptable within the multidisciplinary field of medical ethics. A more ambitious undertaking, however, is to suggest that the theologically trained medical ethicist can in fact offer a fundamentally distinctive contribution to such multidisciplinary and pluralist-based discussions on medical ethics issues.

At first glance, any connection between problems of clinical trial informed consent and motifs such as love and justice or the treatment of strangers may seem irrelevant within a system of diverse religious thought, and especially so to those without religious commitments of any kind. For
the thesis to be valid, i.e., for the theologically trained medical ethicist to be uniquely qualified to provide insight into the reality of clinical trial informed consent, a method must be available that insures there is a plausible connection between the categories of the paradigm and the notions of love and justice offered in service of the categories.

Such a method has been provided by theologians who have argued that there exists a correlation between questions raised by humans and answers provided by theological thought. This "method of correlation" has been explicated primarily by Paul Tillich, and to a lesser extent by Langdon Gilkey and Wolfhart Pannenberg, among others. Essentially, the theological "method of correlation" argues that there is a mutual interdependence between humanity’s existential questions and the answers to these questions that may be provided by theological thought. Utilizing this "method of correlation" as a conceptual model, the dissertation will argue that the concepts of love and justice may be correlated as solutions to problems inherent in each clinical trial informed consent category. The theologically trained medical ethicist may thus provide instructive guidance in clinical trial informed consent analysis, in terms not only of examining salient practices
and potential problems, but also of suggesting viable changes in the paradigm’s implementation.

Clearly, clinical trial informed consent is neither a religious issue nor the exclusive domain of the theologically trained medical ethicist. However, the dissertation’s reliance upon theological thought and curricula will not be a case of forcing the field of religious studies into an issue in which it doesn’t belong. Rather, I will demonstrate that the categories of the clinical trial informed consent paradigm possess an affinity to the notions of love and justice—notations that are explored considerably during the theologically trained medical ethicist’s education and career. Thus, the theologically trained medical ethicist may positively inform discussions on clinical trial informed consent, and therefore may help facilitate implementation of policies and practices that insure a more ethically valid informed consent process in clinical research.

Structure of the argument

The methodology and structure of the dissertation’s argument are as follows: Chapter one introduces the topic and the basic claims and assumptions of the study. Chapter one also contains a review of the relevant literature of the three basic categories of informed consent, the realities of
human experimentation, and the method of correlation to be used in the research and analysis. Also, Chapter one will outline the importance and timeliness of the dissertation's theme.

Chapter two will offer an explication of the role of the clinical trial in the American system of drug development, and will demonstrate salient differences between the research and treatment models of medical practice. Chapter two will also provide a detailed explication of the clinical trial informed consent paradigm categories of recruitment, the notion of outsider, and human experimentation. Finally, Chapter two will discuss relevant criticisms of informed consent theory and practice, and apply these criticisms to the clinical trial scenario.

Chapter three will contain the heart of the dissertation’s analysis of clinical trial informed consent. In this chapter, I will analyze each component category of the clinical trial informed consent paradigm from the perspective of identifying each category’s underlying principles and concepts, and demonstrate their relationship to a valid research informed consent process. This analysis will reveal that the paradigm categories of recruitment and the outsider status of the potential clinical trial subject collapse into issues of background institutional structures and care for the stranger or outsider. The third paradigm
category, that of the human experimentation element of the clinical trial, bolsters the argument that deficiencies in clinical trial informed consent systems and methods of administration should be addressed by concerned medical ethicists. Finally, Chapter three will demonstrate an affinity, or correlation, between the clinical trial informed consent paradigm and the love and justice explications of Paul Ramsey and John Rawls, and will validate the dissertation's claim that the theologically trained medical ethicist is uniquely qualified to offer advice and guidance on the timely issue of clinical trial informed consent.

Having demonstrated the potential benefit of the theologically trained medical ethicist's participation in the clinical trial informed consent discussion, I will in Chapter four offer prescriptive suggestions as to how more valid informed consent processes may be effected in clinical trials. These suggestions will reflect the affinity, or correlation, between the clinical trial informed consent paradigm categories and the love and justice explications of Paul Ramsey and John Rawls.

Review of the literature

The literature for the dissertation will be reviewed within the three basic categories of informed consent, human
experimentation, and the theological method of correlation. This will provide an overview of the major relevant literature upon which the dissertation's arguments are based and formulated. Subsequent chapters will introduce more specific references, including those related to the thought of Ramsey and Rawls, which are needed to further develop the dissertation's claims.

The first literature category will address the theoretical and historical particulars of informed consent. This section of the literature review will provide insight into the true spirit of informed consent—a critical understanding both for examining and explicating potential barriers to its implementation as well as for providing prescriptive suggestions. In keeping with the dissertation's claim for significance in the field of religious studies, a subsection of this category will explore the thoughts of those who have considered the relationship between informed consent and theological thought. The second literature category, that of human experimentation, will provide a framework for understanding the nature and history of the use of human beings in medical research. This review will be structured around a historical appreciation of both ethical and unethical human experimentation, as well as current recommendations and guidelines for the proper ethical treatment of human
subjects. The third and final category will address the theological method of correlation, which will serve as the dissertation's conceptual model for explicating the correlative relationship that exists between the notions of love and justice and the clinical trial informed consent paradigm categories of recruitment, outsider, and human experimentation. This section of the literature review will focus primarily on the thought of Paul Tillich.

Informed consent

Informed consent has been described as the "central priority of medical ethics," as well as a "canon of loyalty" uniting the parties in medical research. Grounded in the moral principle of autonomy, valid informed consent provides not only adequate disclosure of the risks and benefits of the proposed research project or medical intervention, but also the opportunity for the individual to choose freely whether to participate in the research or approve the treatment. In essence, informed consent allows the individual patient or potential research subject the opportunity, via the exercise of autonomous choice, to be his or her own decision maker.

Prior to examining the specific informed consent literature, it will be helpful to survey the historical development of informed consent in general. It is necessary
to begin an examination of the development of informed consent within the general context of clinical medicine, as informed consent in research has been a development within, but separate from, this more global perspective.

Scholars do not agree on the exact date that practitioners of medicine began obtaining the consent of patients for therapeutic interventions. A basic problem in determining an accurate history is that the major elements of what we today call informed consent are conspicuously absent from the writings of the prominent practitioners and theorists of medicine. This is not to say that all elements of informed consent are strictly contemporary concepts. Truth-telling, a precursor to modern informed consent, is discussed in the Hippocratic Oath. However, this is primarily in reference to physicians not telling the truth to their patients for fear of the possible adverse consequences of such disclosure.10

One must appreciate that the standard of care provided by the ancient Greek physicians was patterned on a model of beneficence, rather than on autonomous decision making by the patient. It was the physician’s responsibility to diagnose, treat, and hopefully cure the patient, with the patient expected to assume that whatever therapy was effected by the physician was being performed in the patient’s best interest. This beneficence based model, in
which paternalism was not only practiced by the physician but also accepted by the patient, continued to be accepted well into the Enlightenment period, where obedience to the physician was the practical norm. In fact, the first recorded semblance of a recommendation of full disclosure is found in the writings of Benjamin Rush.\textsuperscript{11} It is important to note the distinction, however, between Rush's advocacy of factual disclosure and the practice of actual consent seeking. One gets the clear impression that although Rush believed in the patient's right to know, and even saw a therapeutic advantage in such disclosure, such a call for factual disclosure did not appreciably deviate from the Hippocratic tradition of essentially blind obedience to the physician. Still, the implementation of such rudimentary forms of disclosure, even without the active consent of the patient, was a critical precursor to what we today appreciate as informed consent for medical treatment.

In 1847, the American Medical Association promulgated its first Code of Medical Ethics, heavily patterned after the full disclosure advocacy of Rush, and also emphasizing the gentlemanly attributes of etiquette. Again, the primary purpose of the code was not grounded in the patient's right to autonomous decision making, but rather in the tradition of beneficence-based disclosure to the patient combined with the furtherance of a positive image for the physician.\textsuperscript{12}
At least two scholars have critically examined the development of informed consent in the nineteenth and twentieth centuries, and have espoused divergent views on its prevalence or lack thereof. Historian Martin Pernick concludes that informed consent was alive and well in the nineteenth century, although admittedly modifying our current definition to arrive at this assertion. For instance, Pernick admits that nineteenth century consent practices, such as those based on the American Medical Association's 1847 Code of Medical Ethics, were beneficence-based rather than autonomy-based. Psychiatrist and legal scholar Jay Katz, on the other hand, asserts that any appreciable element of informed consent was non-existent until the middle of the twentieth century. Katz' working definition of informed consent is more closely aligned with the contemporary model, i.e., factual disclosure coupled with autonomous decision making. The opinions of these two scholars are not as far apart as one might suspect, especially when one realizes that Pernick, because of medicine's paternalistic climate in the nineteenth century, considered full disclosure to be equivalent to informed consent.

Both Pernick and Katz agree that our current understanding of informed consent was born in 1957, when the term was first used in American case law. Extended societal
forces have since shaped the concept of informed consent into today's notion of autonomous choice based upon appropriate disclosure of relevant information.\textsuperscript{15}

Again, the development of our current concept of informed consent occurred within the context of clinical medicine. As previously mentioned, any historical survey of the concepts and practices of informed consent is necessarily based on a consent to the therapeutic intervention model, rather than to research informed consent per se. The historical development of informed consent in research practices is of much more recent vintage, but nonetheless shares the same basic premises of factual disclosure and autonomous choices as found in informed consent for medical treatment. Although there are isolated references to research informed consent throughout modern history, it was only after the heightened awareness of the atrocities of Nazi Germany, which were often instigated under the guise of scientific investigation, that widespread concern for what is now considered research informed consent became prevalent.

Informed consent, both for medical treatment and for research, has now reached a certain level of maturity of definition. However, one must not presuppose that the operational aspects of informed consent are the same for research as for treatment.
Most scholars and clinical investigators agree that stricter standards for informed consent apply to the relationship between the clinical investigator and the research subject than that between the physician and his or her patient. The specific elements of research informed consent were adopted in 1981 by the United States Department of Health and Human Services:

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 subject's 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.16

Robert J. Levine has correctly described the principle that the major underlying distinction between obtaining informed consent in the treatment as opposed to the research model is that the potential research subject must be informed that, if consent to participate in the project is granted, he or she will in part be used as a means to an end.17 Such notification does not, for Levine, spell a fundamentally different purpose between informed consent for research and for medical treatment. Arguing that the two models are more similar than different, Levine asserts that "the primary purpose of informed consent is to be responsive to (to uphold and embody) the ethical principle of respect for persons."18 Levine does not make clear, however, that his argument is highly theoretical. The purpose of informed consent may indeed be to keep the principle of respect for persons intact. However, in practice informed consent for research is utilized for a totally different function than informed consent for treatment—a function supported by my earlier assertion, which will be more fully developed and demonstrated in subsequent chapters, that clinical trial
informed consent is basically a vehicle for recruiting outsiders into the realm of human experimentation.

Levine is not unmindful of the disparity between the research and treatment models of informed consent. He correctly points out that research informed consent is generally viewed as something that takes place at one meeting between the investigator and the potential subject, and that treatment informed consent generally occurs over a greater time span. Further, Levine aptly describes the difference that autonomy plays in the physician-patient versus the investigator-subject relationship. Clinical investigators attempt to avoid recruiting subjects with limited autonomy, except when clearly unavoidable because of the nature of the disorder being studied, e.g., Alzheimer's Disease. Medical practitioners, on the other hand, because of the specific nature and symptoms of many diseases, must recognize diminished autonomy as a frequent patient characteristic. However, Levine dismisses these differences too quickly, preferring his theoretical notion of the purpose of informed consent and not fully appreciating that the differences on the operational level translate over time to differences in the function of the two informed consent models.

Ruth R. Faden and Tom L. Beauchamp, in A History and Theory of Informed Consent, have provided a comprehensive
history of informed consent and an explication of the rationale for specific consent policies. With a primary goal of satisfactorily answering the question, "What is informed consent?" Faden and Beauchamp offer a detailed analysis of informed consent's conceptual framework, including philosophical and legal precursors and ramifications.

Part I of *A History and Theory of Informed Consent* focuses on relevant concepts of moral and legal theories. Framing the basic ethical issues involved in the informed consent process around philosophical and legal thought provides a foundational structure that allows an examination into the reasoning involved in informed consent theory and practice.

In Part II, Faden and Beauchamp shift to an "interpretative history" of informed consent policies and precursors from the ancient Greek codes up to today's "New Medical Ethics." Included in this section is a detailed exposition of the relationship between legal doctrine and the evolution of informed consent procedures. Faden and Beauchamp note that the overriding principle used to justify informed consent has generally been that of self-determination.
The notion of self-determination is further explicated in Part III, which shifts to a conceptual analysis of the nature of informed consent. Particularly noteworthy in this section is the treatment of the principle of autonomy, where Faden and Beauchamp demonstrate that the true cornerstone of informed consent is the practice of an autonomous action in which the patient authorizes the physician to perform a treatment procedure or institute therapy or research. In order to be authentic, such autonomous activity must meet the three conditions of intentionality, understanding, and noncontrol.

Faden and Beauchamp note the differences between informed consent for treatment and for research, asserting that the latter has had a "revolutionary impact on day-to-day activities." However, it is clear from Faden and Beauchamp's argument that this impact lies in the domain of the obtaining of research informed consent, and not so much in its practice as autonomous decision making based on factual disclosure.20 The solicitation of informed consent by researchers may well be a higher priority than in the treatment paradigm. However, as I will argue in subsequent chapters, this emphasis on obtaining informed consent does not necessarily translate into a more valid informed consent process, and in fact is more often a hindrance to the notion itself.
Although not presuming prior familiarity with the concept of informed consent, the scope and depth of *A History and Theory of Informed Consent* establish it as a useful reference for scholarship in both informed consent for treatment and for research. However, the two models are treated by Faden and Beauchamp more as variations of a common theme, rather than as separate paradigms. One can expect a continued lack of appreciation for the unique operational function of research informed consent so long as similarities between the two models are stressed and critical differences are not fully explored.

Five years after his comparison of the two models of informed consent, i.e., treatment and research, Levine offered an additional useful explication of research informed consent in *Ethics and Regulations of Clinical Research*. In this later volume, Levine correctly recognizes and describes research informed consent as a multi-faceted process. In addition to providing useful background material on the ethical and legal origins of research informed consent, Levine raises many issues that are applicable to the focus of the current study. For instance, Levine argues that:

...throughout most of this book I have called attention to a large number of barriers to achieving the goals of informed consent. Now I wish to mention some that, although very important, do not seem to fit conveniently in any
other section. These obstacles are rooted in the ethos of the medical profession as it exists in the United States. It is this ethos that determines who doctors are and who patients are and what they expect of each other.\textsuperscript{52}

Specifically, Levine argues that barriers to effective informed consent exist within the categories of authority, autonomy, and uncertainty.

The notion of authority as a category is exemplified by the discrepancy in the levels of trust between the physician and the patient. On the one hand, patients are conditioned or expected to trust their physicians. This trust is presumably justified by the altruistic tradition of the medical profession. On the other hand, physicians are conditioned or expected to distrust, or at least not actively trust, their patients. For example, physicians are taught early in their training to be suspicious of malingering by patients.

Concerning autonomy, Levine argues for a newer, more comprehensive definition of the concept, and quotes an earlier argument of Jay Katz:

\begin{quote}
Immanuel Kant, in restricting his conception of autonomy to capacities of reason, without reference to human beings' emotional life and their dependence on the external world, projected a vision of human nature that estranged his principle from human beings and the world in which they must live. That Kant did so deliberately and with full awareness, because he wished to isolate and abstract a single aspect of human psychology,
i.e., rationality, into its pure form, is a separate matter. What matters here is the Kantian principle of free will, since it is based on this single aspect of human psychology, makes, if applied to actual situations, demands for human conduct that human beings cannot fulfill.23

Since the more traditional notions of autonomy do not take into consideration the psychological realities of physicians and patients, Levine argues along with Katz that these "...conscious and unconscious, rational and irrational forces...(which) shape all thought and actions..."24 be taken into account in any new, more comprehensive definition of autonomy.

The third broad barrier to valid informed consent, that of uncertainty, is exemplified by the ability of scientific research to demonstrate more of what is not known rather than what is known. In other words, every major breakthrough in scientific knowledge leads to a simultaneous awareness of ignorance. Although not mentioned by Levine, AIDS provides an excellent model for this concept. The isolation of the virus responsible for the Acquired Immune Deficiency Syndrome (AIDS) was rightly considered a major breakthrough in modern medicine. However, being able to describe and name the cause of AIDS served only to heighten awareness that modern medicine initially knew little about transmission, prevention, and certainly a possible cure for this deadly malady. Such ignorance is useful if used to
challenge the mind to pursue appropriate answers to important questions. The problem arises, according to Levine, when physicians and presumably investigators refuse to share this awareness of ignorance with their patients and potential research subjects. Rather than openly acknowledging the uncertainties of medical practice and research, it is all too easy for the physician to avoid such appearances of ignorance and vulnerability.

In addition to the useful discussion of barriers to informed consent, Levine offers valuable insight into such areas as specific standards for valid informed consent, strategies for the appropriate negotiation of informed consent, and the informed consent documentation process. All of these contingencies are critical in any study of clinical trial informed consent, and will be referred to in appropriate sections of the current inquiry.

Levine's explication of informed consent provides insight on at least two levels. First, Levine produces an overview of the regulations and procedures of informed consent—an examination that is not limited to theory but also includes practical applications. Second, and considerably more important, Levine examines informed consent as ethical process rather than as strictly regulatory activity. His focus is on the spirit and intent of the requirements for informed consent, but without
sacrificing the necessary but highly problematic reality of research informed consent documentation. Thus Levine is able to address both the ethical priorities and regulatory requirements of clinical research without emphasizing one to the detriment of the other.

Katz has critically examined the relationship between physician and patient, and has concluded that true informed consent is more myth than reality:

...disclosure and consent, except in the most rudimentary fashion, are obligations alien to medical thinking and practice. Disclosure in medicine has served the function of getting patients to 'consent' to what physicians wanted them to agree to in the first place. 'Good' patients follow doctor's orders without question.²⁶

In The Silent World of Doctor and Patient, Katz argues that consent seeking in medicine is limited to describing benefits and risks of procedures, rather than open discourse concerning possible alternatives. In other words, physicians merely use the consent process as a vehicle to get patients to comply with their recommended therapy.²⁷ Essentially, Katz argues that little progress has been made in informed consent practices since the eighteenth century, when, as referenced earlier in this chapter, informed consent was for practical purposes a symbol of beneficent paternalism.
If one assumes Katz to be correct in his assessment of consent in treatment, how applicable is this argument to research? More particularly, is there a danger of this paternalistic manipulation of the potential research subject? First of all, the more recent history of human experimentation leads to the assumption that research has been conditioned by the historical development of informed consent much more than has medical treatment. That is, by the time large-scale studies were carried out in humans, the courts and governing bodies had already laid the groundwork for informed consent. Also, the very nature of research, as opposed to treatment, has no doubt instilled in the minds of clinical investigators the necessity for proper informed consent. This is not to say that Katz' argument does not apply to research. The silence that Katz so aptly describes can be just as prevalent in the research environment as in the treatment clinic or hospital. Many patients place themselves unreservedly under the protection and care of their personal physician. Should a physician recommend participation in a research project to such a patient, it is clear that valid informed consent could well be compromised.

Katz suggests that a continuous dialogue between physicians and patients will help assure that the patient is allowed the freedom of autonomous choice. Without such dialogue, Katz asserts, physicians will continue to make
therapeutic and personal decisions for their patients. The various options available will not be discussed unless more open communication is effected between both parties. Although some patients may appear to want their physician to make all the decisions, such an attitude does not excuse the absence of true informed consent in the process. Although Katz refers specifically to the treatment scenario, it may just as well be assumed that without dialogue between investigator and potential subject, such persons may well find themselves "volunteered for" in clinical trials. In fact, the degree of voluntarism present in the obtaining of research informed consent is extremely difficult to assess in any given individual. This reality has led Howard Spiro, noted gastroenterologist both as clinician and researcher, to argue that a physician with a close relationship to a patient can persuade the patient to do almost anything, presumably including participating in an experimental project.

This scenario of research informed consent is all the more troublesome when one realizes that research concerning Alzheimer's Disease, senility, and similar maladies is of necessity performed in less than fully competent subjects. Many of these individuals in our society are in strong dependency relationships, especially those living with or near their children or other relatives. Patterns of
authority and threats of withdrawal of support, both real and imagined, are major factors influencing the ability of such individuals to exercise their autonomy. It must be appreciated by the clinical investigator that the patient qua potential subject might perceive the physician as interpreting his or her possible refusal to participate in a research project as an indication that the physician's judgment is no longer trusted or that the patient wants the professional relationship to end. Such patients may thus make a decision to participate in a clinical trial based upon the desire to continue their therapeutic relationship with the physician. Of course, a valid consent process will address these issues by assuring that refusal to participate will not affect the medical care afforded the patient or the relationship between the patient and the physician.

Further, research informed consent is also problematic for the dying patient—a scenario on the increase because of technological breakthroughs in sustaining the lives of the dying, as well as of the discovery of promising drugs for malignancies and other terminal conditions—compounds that must of course be tested in human subjects. Although the competency of the dying patient is not necessarily compromised, one must, especially in the research scenario, be mindful of the fact that it might be. The terminally ill are, after all, frequently desperately seeking a cure for
their disease. Does the understandable eagerness on the part of the dying person to "try anything" translate into the potential for abuse of this population by investigators under pressure to reach clinical trial enrollment goals? Similarly, does this eagerness invite hasty enrollment in a trial of a possibly effective agent, without an appreciation for the fact that the agent may indeed be ineffective and hence worse for the potential subject than whatever conventional therapy might be available?

The use of laetrile in cancer is an excellent example of this phenomenon. While there is no evidence that the administration of laetrile is harmful per se to the cancer patient, the fact remains that whenever patients discontinue conventional cancer therapy to pursue laetrile treatment they effectively end any chance that the conventional therapy may indeed work. Although the chances of conventional therapy working may indeed be mathematically slim, the odds are nonetheless higher than with a totally ineffective, albeit admittedly directly harmless, agent. Again, one must not necessarily exclude the terminally ill from consideration for research projects, but must appreciate the altered decision making apparatus that may be present in such individuals.

Regardless of the relative competency of the potential subject, one must appreciate that the implementation of a
valid clinical trial informed consent process consists of much more than merely the legalistic meeting of HHS guidelines on the written consent document:

...the process of obtaining 'informed consent', with all its regulations and conditions, is no more than an elaborate ritual, a device that, when the subject is uneducated and uncomprehending, confers no more than the semblance of propriety on human experimentation.  

Even those who might take issue with Franz J. Ingelfinger's above assertion that informed consent is no more than a ritual and offers little or no protection to the research subject must stop and consider the potential for abuse and failure in the entire clinical trial informed consent transaction.

Informed consent and theological thought

Since the dissertation is concerned with the claim of a unique qualification for the theologically trained medical ethicist to analyze the clinical trial informed consent paradigm and to subsequently suggest remedies for the critical deficiencies in the implementation of the paradigm, it will be useful to note what other thinkers have discovered when considering the relationship between theological thought and informed consent. Paul Ramsey, for instance, has offered a useful explication of informed consent for both medical treatment and research. Arguing
that a "reasonably free and adequately informed consent" is a crucial element in the notion of morally right action in medical practice, Ramsey further asserts that informed consent is in essence a statement of fidelity between the physician and the patient or subject:

Fidelity is between man and man in these procedures. Consent expresses or establishes this relationship, and the requirement of consent sustains it. Fidelity is the bond between consenting man and consenting man in these procedures. The principle of an informed consent is the cardinal canon of loyalty joining men together in medical practice and investigation. In this requirement, faithfulness among men—the faithfulness that is normative for all the covenants or moral bonds of life with life—gains specification for the primary relations peculiar to medical practice.32

Relying upon the structure of Reinhold Niebuhr's defense of democracy, Ramsey suggests that consent is possible due to one's ability to become a joint adventurer with another person, and is simultaneously necessary due to the individual's propensity to overreach that same relationship. Viewing the consent relationship as a partnership rather than as a contract, Ramsey asserts that the spirit of true co-adventuring is manifested by appreciating informed consent as a "continuing and repeatable requirement."33

Although he admits that obtaining a "reasonably free and adequately informed consent" is not a simple task, Ramsey nonetheless insists that such requirements are
especially necessary for informed consent in human research. Otherwise, the temptation to circumvent a valid informed consent process could be heightened by the investigator's realization that much aggregate good may come from his or her experiment. In other words, clinical investigators may be swayed by beneficent utilitarianism into sacrificing valid informed consent on the individual level so that major scientific advances may be attained. Ramsey warns that such potential for good, regardless of the motives of the investigator, must never be a factor in determining the validity of any exception to informed consent in human research.34

Ramsey’s thought on issues of medical ethics should not be taken out of context from his earlier pronouncements in the field of theological ethics. In fact, David Smith argues that Ramsey’s later work in medical ethics should optimally be read in light of his "prior faith commitments," for it is here that one finds the seeds of Ramsey’s notion of covenant fidelity.35 Chapter three will provide a more detailed focus both on Ramsey’s theological thought and his later work in medical ethics.

Ramsey is not the only thinker who has applied theological thought to the notion of informed consent, although the Judeo-Christian tradition of medical ethics does not specifically call for consent. John Wilkinson, for
instance, has argued that informed consent is akin to the Christian notion of reciprocity. This notion, which has its roots in Matthew 7:12, or the Golden Rule, directs that one should treat others only as one would like to be treated by them. Wilkinson translates this concept into the human experimentation arena by suggesting that an investigator should never direct an experiment in which he or she would not wish to participate as a subject. One could add to Wilkinson's thought the notion that if indeed an investigator would be willing to participate as a subject in a given experimental study, this is not a sufficiently justifiable reason to assume that a patient or potential subject should therefore necessarily be willing to participate.

Catholic medical ethicists Benedict M. Ashley and Kevin D. O'Rourke see a direct relationship between informed consent and the notion of a well formed conscience, which is described in the Second Vatican Council as the process by which "law is made known which is fulfilled in the love of God and one's neighbor." Ashley and O'Rourke assert that this directive translates into a responsibility

1) to learn the facts about the medical condition and other circumstances of the person involved, 2) to determine in accord with an objective value-
system the needs and rights of the people involved; and 3) to come to a concrete, personal decision in spite of disagreement or pressures from others.38

Suggesting that the theologically trained medical ethicist is uniquely qualified to inform a discussion on clinical trial informed consent is not without challenge or even controversy. The idea that theological insight is relevant in such affairs "is wont to be dismissed by a short and simple argument."39 Clearly, thinkers such as Ramsey have demonstrated that there is a relationship between informed consent and specific theological and philosophical precepts. I will attempt to further define this relationship within the three specific categories of the clinical trial informed consent paradigm, i.e., recruitment, the notion of outsider, and the reality of human experimentation.

The ethics of human experimentation

The use of human subjects to help unlock scientific riddles is certainly not a recent phenomenon. Claude Bernard, in his landmark Introduction to the Study of Experimental Medicine, refers to the second century B.C. practice of using condemned prisoners for medical experimentation.40 However, references to human experimentation before the eighteenth century are sketchy at
best, and quite possibly influenced as much by legend as by fact.

Much of the human experimentation of the eighteenth and nineteenth centuries centered around potentially deadly infectious diseases such as smallpox and cholera. Interestingly, much of this research was performed on prisoners and children—two populations that have attracted considerable attention in recent medical ethics debates. However, it was the outcry over World War II Nazi atrocities that finally gave birth to the present concern over the ethical treatment of human research subjects. Although there is thankfully a significantly different moral and scientific basis between the Nazi concentration camp experiments of the 1940's and well-controlled clinical trials of today, the fact that both scenarios involve human subjects being used for research activities invites at least a brief glimpse of the actions, methods, and rationalizations of the Nazis.

Andrew Ivy distinguishes between Nazi procedures that were designed to answer a legitimate scientific question and those that had no such objective. Nonexperimental crimes made up the bulk of Nazi atrocities, as these included the genocidal exterminations of Jews, Poles, Russians, and gypsies—groups deemed by the Nazis to be subhuman. Although affecting considerably fewer victims, Nazi war
crimes with at least some semblance of scientific inquiry as their basis nonetheless play a major but clearly emotionally disturbing role in our present understanding of what activities constitute the boundaries of ethical human experimentation.

The Nazi typhus experiment, because of its prima facie justification as a method to develop a vaccine for the deadly typhus virus, provides an excellent example of the unethical pursuit of knowledge for a presumably worthy cause. In this project, the typhus virus was injected into two prisoners. After these persons became acutely ill, their blood was injected into other prisoners, thus keeping the virus alive. The typhus vaccine experiment was not technically dissimilar to modern clinical trials, as evidenced by the use of a clearly defined scientific protocol.42

Although there are obvious similarities between the typhus vaccine experiment and current clinical trials, e.g., the use of control groups, there was of course one major difference. The Nazis did not utilize anything even vaguely resembling a valid informed consent process. Although this involuntary nature of subject participation is well known, this neglect is particularly interesting when one considers that a 1931 German law outlined the rights of human research subjects--rights that explicitly included the notion of
informed consent." In fact, such laws were on the books
during the entire Third Reich."

Even during the Nuremberg trials, there is evidence
that the Nazi doctors justified their failure to obtain
informed consent from the prisoners. For instance, in a
final plea for defendant Karl Brandt, Robert Servatius
observed that:

It has been repeatedly shown that the experiments
for which no consent was given were permitted with
the full knowledge of the government authorities.
It is further shown that these experiments were
published in professional literature without
meeting any objection, and that they were even
accepted by the public without concern as a normal
phenomenon when reports about them appeared in
popular magazines."

The trials of the Nazi doctors resulted in Ivy’s
articulation of perceived universal norms for ethical
practices of human experimentation:

1) The voluntary consent of the person on whom the
experiment is to be performed must be obtained.

2) The danger of each experiment must have been
investigated previously by means of animal
experimentation.

3) The experiment must be performed under proper
medical protection and management."

Paul J. Appelbaum points out that the Nuremberg trial
judges relied heavily upon Ivy’s testimony in writing their
final judgments against the Nazi doctors." These
judgments, when codified and promulgated, became known as the Nuremberg Code. Of particular interest, although certainly not surprising, is the fact that the first ten sections of the Nuremberg Code specifically address informed consent in human experimentation.48

Although clearly a major first step toward the establishment of a universal code of human research ethics, there were discernible problems with the Nuremberg Code from the outset. First, the code was essentially unenforceable in the international research milieu.49 Second, the requirement for informed consent in all circumstances would seemingly disallow legitimate medical research on persons of questionable competence.50 These concerns led to the 1964 adoption of the Declaration of Helsinki, which differed from the Nuremberg Code in two significant ways: 1) by distinguishing between "medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research,"51 and 2) allowing proxy consent in the case of questionably competent research subjects.52 Notwithstanding its allowance for waivers of research informed consent in some cases, the Declaration of Helsinki has stood the test of time. It is the cornerstone of current United States Food and Drug
Administration (FDA) regulations concerning informed consent in clinical trials.\textsuperscript{53}

This literature on human experimentation, and other sources that will be referenced as the study unfolds, provides useful background material not only for the third category of the clinical trial informed consent paradigm, i.e., the reality of clinical trials as exemplars of human experimentation, but also for the entire notion of clinical trial informed consent as a distinctively separate issue from informed consent for medical treatment. Acceptance of the clinical trial as an exercise in human experimentation is critical in establishing and maintaining the necessary distance between the two models.

Paul Tillich and the method of correlation

As outlined earlier, I will depend upon the theological notion of correlation to provide a model for the connection of clinical trial informed consent categories to the theological and philosophical concepts with which they possess an affinity. This method, when used in theological argument, connects existential issues such as "the finitude of the human condition" with theological notions such as "God as creator of the universe." Correlative symbols are the vehicles for such connections. Such symbols link the
existential question with the theological answer in a manner that does not presume specific faith commitments.

Paul Tillich's method of correlation is, among theologians, the best known. Tillich's primary mission was to "make Christianity understandable and persuasive to religiously skeptical people." In an effort to achieve this goal, Tillich argued throughout his career that the secular and the sacred have business together. The Tillichian method of correlation allows the introduction of theological concepts without presupposing a confessionally oriented theistic grounding in the hearer of the message—a notion that, because of the pluralistic society in which we live, is critical to the theologically trained medical ethicist.

Tillich, as a systematic theologian, did not directly address issues of medical ethics in his career. However, his introduction of theological concepts into discussions on meanings and values is particularly relevant to the theologically trained medical ethicist, who is challenged to offer faith-informed guidance to a pluralist, secular world. In fact, the success of the theologically trained medical ethicist depends largely upon his or her ability to reach over into the bounds of secularism without forfeiting the models and symbols of faith.
Tillich was born in 1886 in Starzewedd, Germany. The son of a conservative Lutheran pastor, Tillich studied theology at Berlin, Tubingen, and Halle before receiving his Ph.D. in 1910 from the University of Breslau. After serving as a pastor in the Evangelical Lutheran Church, Tillich became a German Army chaplain in 1914. According to his biographers, four years of war radically changed Tillich, as "the traditional monarchist had become a religious socialist, the Christian believer a cultural pessimist, and the repressed puritanical boy a 'wild man'."55 Tillich, however, interpreted these changes in himself as changes in Western civilization.56

Tillich enjoyed a series of appointments to the religious studies faculties at Berlin, Marburg, Dresden, and Frankfurt. In 1933, because of his anti-Nazi ideology and involvement with the religious socialist movement, Tillich was forced to leave Germany. With the assistance of Reinhold Niebuhr, Tillich settled in New York City with a faculty appointment at Union Theological Seminary. After spending the next fifteen years in relative obscurity, Tillich published in 1951 the first volume of Systematic Theology, which ultimately brought him considerable exposure. Tillich retired from Union in 1955, and accepted a position at Harvard University. From Harvard, he went in 1962 to the University of Chicago, where in 1963 he
published the third and last volume of Systematic Theology. Tillich died in 1965.

In his attempt to make Christianity intelligible to a secular world, Tillich developed his method of correlation as a system that assists the "unavoidable duty of every theologian to relate the biblical message to his contemporary situation." Tillich begins each section of his Systematic Theology by analyzing one of humanity's central existential problems. After thoroughly explicating the issue in terms of its relationship to mankind's very existence, Tillich demonstrates the salience of Christian thought in providing an answer to the particular issue. Central to Tillich's method of correlation is the notion of "answering questions." Clearly, providing answers to important questions is seen by Tillich as the theologian's basic task, especially if the theologian's mission is apologetic. Further, Tillich does not claim that his method of correlation is his own invention:

Systematic theology uses the method of correlation. It has always done so, sometimes more, sometimes less, consciously, and must do so consciously and outspokenly, especially if the apologetic point of view is to prevail. The method of correlation explains the contents of the Christian faith through existential questions and theological answers in mutual interdependence.

Tillich identifies three distinct usages of the term "correlation." It may refer to the correspondence of
"different series of data," which in theological terms may mean correspondence between religious symbols and "that which is symbolized by them." Second, correlation may refer to the "logical interdependence of concepts," such as the connection between human and divine concepts. Third, correlation may refer to the "real interdependence of things or events in structural wholes," which is translated into theological terms by connecting man's "ultimate concern and that about which he is ultimately concerned."⁶⁰

In Tillich's system, questions and answers are not entirely distinct entities. Answers are formulated under the guidance of the questions, and the questions themselves are formulated and reformulated under the guidance of the theologically-based answers. However, this interdependence of the questions and answers does not signify a lack of structure or even a lack of separation in Tillich's systematic analysis of mankind's existential questions and their corresponding theological answers:

The method of correlation requires that every part of the system should include one section in which the question is developed by an analysis of human existence and existence generally, and one section in which the theological answer is given on the basis of the sources, the medium, and the norm of systematic theology. This division must be maintained. It is the backbone of the structure of the present system.⁶¹
William E. Hordern has suggested that the essence of Tillich's system is basically a philosophical analysis of a given existential question, followed by an answer that springs forth from Christian revelation. The answer comes only after "the problem has been probed to its final depth and its relation to man's existence and being becomes clear." David Kelsey views Tillich's analysis as an attempt to mediate between religion and culture, especially in regard to historical Christianity and contemporary culture. In so doing, Tillich has been accused of "translating the content of Christian faith without remainder into the deepest conviction of...secular culture." Most notably, Barth suggests that Tillich's question/answer dialectic is deceptive in principle as well as in application. Others however, such as Tracy, Gilkey, and Pannenberg, have embraced correlation theology at least to some degree in their own thought.

In Part I of Systematic Theology, Tillich correlates the question "How can we know with certainty any humanly important truth?" with the theological symbol Logos. In essence, Part I consists of Tillich's views on knowledge, truth, and reason. Arguing that mankind's ability to know and the use of that ability permeates every human transaction, Tillich demonstrates that the quest for knowing truth always results in meaninglessness. People attempt to
understand reality with their "ontological reason," which is
distinct from "technical reason." Ontological reason is the
structure of the mind. Technical reason is relegated to
ordinary capacities for solving problems. Ontological
reason, while a richer variant than technical reason, is
nonetheless finite. That is, persons fluctuate between
knowing as a result of self reliance (autonomy) and knowing
as a result of relying on an outside authority figure or
tradition (heteronomy). 67

The fluctuation between autonomy and heteronomy,
rooted in what Tillich refers to as a conflict between the
structure and depth of reason, gives rise to questions
relative to humanity's ultimate concern, or "that which
grounds meaning in life." 68 Tillich asks how persons can
know any important truth—a question answered by the
religious symbol of Jesus as the Logos. Jesus is the
"concrete instantiation of the presence of the ground of
meaning in life." 69

Part II of Tillich's system relates to the notions of
being and finitude, and the relatedness of these concepts to
God. For Tillich, "it is the finitude of being which drives
us to the question of God." 70 The finitude of being is
represented and known by the feelings of guilt and
meaninglessness from which persons suffer. It is at this
point that we discover Tillich's ontology. Rather than
follow the lead of others whose analyses of what it means "to be" point to the reality of God, Tillich's ontological analysis demonstrates our own finitude. Our being is inherently and constantly frustrated and threatened by non-being.

In spite of being constantly threatened by non-being, mankind is amazingly able to stay together and resist the perilous threat. Somehow we are able to function relatively efficiently even in the face of the power of non-being. The obvious question that is raised by this scenario is "Whence comes the power to resist the threats of non-being?" For Tillich, the answer to this question is found in the concept of God. Tillich's God is not anthropomorphic, but rather is based upon his notion of ultimate concern. That which ultimately concerns us is our God. Specifically, Tillich argues that the Christian symbols of God, particularly those dealing with the notion of God as Creator, best answer the question as to the source of the power of non-being. These symbols point to a God of creation—a God on whom our very existence, being, and power depend.

In Part III of his system, Tillich shifts away from matters of the "essential nature" of humanity and toward more existential topics. Tillich reminds us that the root word for existence is existere, or to "stand out." This immediately gives rise to the question "To stand out of
what?". To answer this existential question, Tillich again turns to his ontology:

...standing out in the sense of existere means that existence is a common characteristic of all things, of those which are outstanding and of those which are average. The general answer to the question of what we stand out of is that we stand out of non-being...If we say that something exists, we assert that it can be found, directly or indirectly, within the corpus of reality. It stands out of the emptiness of absolute non-being. 74

Because we stand out from our essence, we are by nature estranged from the power of being. This estrangement may take on the form of sin, unbelief, guilt, meaninglessness, and even death. Our world becomes chaotic, and our relationships with others and within ourselves break down. 75

Out of this morass of guilt and chaos comes the question "How can man become a New Being?". Tillich correlates this question with the religious symbol The New Being as Jesus the Christ. Kelsey describes Tillich's relationship between accepting Jesus as the New Being and mankind's chaos as a "reconciliation with the power of being and, along with that reconciliation with others and oneself." 76 In Jesus as the power of New Being, we find a mediation of humanity's estrangement and all of its manifestations.
In Part IV of his system, Tillich is concerned with the actualization of life itself, which includes life's ambiguities and the quest for an answer to those ambiguities. The actuality of the individual's life is in the synthesis of the essence and existence of life—two concepts explicated by Tillich in Parts I and II. Central to the notion of life's actuality is the reality of the spiritual realm. For Tillich, "spirit" refers to "the unity of life-power and life in meaning," or in condensed form, the "unity of power and meaning." 

There are three distinct functions of the spiritual life: 1) self-integration, 2) self-creation, and 3) self-transcendence. All three of these functions, which exist beyond the organic and inorganic realities of life, are ambiguous in nature.

Finally, in Part V of his system, Tillich correlates the theological symbol "Symbol of God" with the historical dimension of life. Although related to Part IV, the historical dimension is treated separately for traditional and practical reasons. Tillich thus maintains the traditionally "independent and extensive treatment" that is generally afforded inquiries concerning the relationship of human history to the notion of the Kingdom of God.
I will come short of suggesting that the relationship between Rawls' and Ramsey's thought reflects a purely "Tillichian correlation", i.e., the questions and answers found within the five parts of Tillich's system, with the paradigm categories of clinical trial informed consent. The difficulty in making such a claim comes not from deficiencies in the correlation per se, nor in the differences inherent in the philosophical questions of Tillich's dialectic as opposed to the more concrete contingencies of clinical trial informed consent. Rather, my reluctance springs in reality from Tillich's own rather vague notion of correlation.\textsuperscript{80}

Simply put, Tillich is difficult to understand. This is as true for his peers as for those less initiated, as is evidenced by G.E. Moore's remark to Tillich following one of the latter's lectures:

\begin{quote}
Now really, Mr. Tillich, I don't think I have been able to understand a single sentence of your paper. Won't you please try to state one sentence, or even one word, that I can understand?\textsuperscript{81}
\end{quote}

John Powell Clayton has concisely summarized the difficulty faced in attempting to frame any problem with a "Tillichian analysis," and also points to why the very notion of a "Tillichian school of thought" is problematic:
Not only have theologians failed to agree regarding the significance of Tillich's method of correlation, they have furthermore failed to agree as to what is meant by 'correlation' in that method. Nor is this state of affairs entirely the fault of Tillich's would-be interpreters: for Tillich himself failed to clarify sufficiently and to disentangle carefully the multiple senses in which he used the term. 82

The difficulty in claiming a strong Tillichian-like correlation does not, however, translate into a weaker argument for Tillich's relevance to the study at hand. The claim for a Tillichian-like correlation is based upon the notion of affinity—in this case the affinity between the clinical trial informed consent paradigm categories and the love and justice reflections of Ramsey and Rawls.

The inclusion of Tillich's thought as a framework is supportive of my basic thesis that the theologically trained medical ethicist is uniquely qualified to offer insight and guidance in the area of clinical trial informed consent. The validity of the thesis does not, however, rest in whether this affinity is in any strict sense representative of all the nuances of Tillich's method of correlation. Rather, my claim is that Tillich, with his insistence that the secular and the sacred have business together, provides a useful framework for positing theological and philosophical constructs over against the secular contingencies with which they possess a relationship. This framework may be employed by the theologically trained
medical ethicist in more clearly explicating the relationship between love and justice and the component categories of the clinical trial informed consent paradigm. Thus the theologically trained medical ethicist, who with Tillich faces the challenge of mediating between faith and cultural or secular issues, may find Tillich's thought to be instructive for formulating and defending ideas.

Importance of topic

The new ground being staked out by this dissertation is not only conceptually interesting, but also can be pivotal for suggestions for change. Appreciating clinical trial informed consent as a fundamentally different paradigm, and demonstrating a correlative relationship between philosophical and theological thought and the categories of the paradigm, invites and allows a more focused and useful critique.

The dissertation helps validate the claims of others that theology and theologically based medical ethics may offer guidance in the field of medical policy and decision making. In the words of Donald W. Shriver, Jr., "...the study of religion does indeed hold promise of making tangible contributions to medical care." Similarly, Kenneth L. Vaux signals the return of the "medical theologian," who has presumably become closeted via an
overwhelmingly passive response to the pluralist influences of our society, and the corresponding temptation "to be all things to all people." 84

James Gustafson poignantly argued in 1979 that the "growth industry" status of medical ethics pushed the previously prolific theologically trained scholars in the field into a situation of either repression, denial or indifference to their theological commitments and training. 85

Earlier, in 1975, Gustafson claimed that a basic failure of the theological medical ethicist was the failure to develop the theological background for one's thought, due in part to one's secular colleague's general lack of interest in such affairs. To introduce theologically grounded argument into secular discussions invites one's colleagues to essentially ignore whatever one may have to say about the specific topic at hand. 86

Gustafson's argument is persuasive, but perhaps points to too great a segregation between theological medical ethicists and their colleagues in medicine and philosophy. Is a person trained in medical ethics in a religious studies department necessarily a theological medical ethicist? Since many such departments are not confessionally oriented, I would suggest that a more appropriate reference, and the
one employed in this study, is that of a theologically trained medical ethicist. The difference is more substantive than a mere semantic manipulation. Such individuals can converse with representatives of other academic disciplines and encounter less resistance than that described by Gustafson, and thus are able to offer distinctive interpretive insight to a pluralist society.

The timeliness of the dissertation's inquiry is apparent when one considers the current movement toward a universal standard for clinical research. The issue of harmonization of Good Clinical Practice (GCP) guidelines, which include informed consent issues, has become a driving concept in global pharmaceutical development. The term harmonization, in this context, refers to the process of coordinating and to a considerable extent duplicating the research, development, and manufacturing requirements of drug companies in the major international markets. The objective of harmonization is quite simply the development and implementation of universal standards for the pharmaceutical industry.

As the 1992 deadline for the formation and empowerment of the European Economic Community (EEC) approaches, a high level of seminar, symposium, and workshop activity has been observed. Although the more purely ethical elements of GCP, i.e., issues of institutional review and informed consent,
are addressed at such gatherings, it is also clear that the primary direction of the dialogue is the implementation of GCP and not specifically whether such implementation is appropriate.

A May, 1990 Montreal symposium entitled "The Clinical Trial in Canada, USA, and Nordic and EEC Countries," produced a comprehensive abstract on the broad concept of ethics in international clinical research. Participants included former FDA Commissioner Arthur Hull Hayes, Yale Institutional Review Board Chairman Robert J. Levine, and former president of the Danish Society of Clinical Pharmacology Eigell F. Hvidberg. The symposium was attended by approximately three hundred industry representatives, regulatory authorities, and scholars.

Rhone Poulenc Vice President Yves Champey expressed optimism in the progress being made toward harmonization:

Considerable progress is...being achieved, especially in the EEC, in harmonizing the various rules, defining Guidelines and Good Clinical Practice, and working toward reorganization of the marketing authorization.

Champey was not unmindful of the problems involved in the harmonization of ethical requirements in clinical trials, pointing out the existence of substantial regulatory and cultural differences among the twelve EEC member countries.
Hayes challenged the audience to reflect on the increasingly international complexion of drug development, both in its scientific and commercial aspects. Although accepting the call for harmonization of GCP requirements as a positive step, Hayes warned that merely applying FDA guidelines to a "universally standardized patient" would amount to attributing to the FDA and the United States "an arrogance which neither wants nor deserves." Pointing out that the FDA system is designed to address the particular needs of the United States, Hayes asserted that the specifics of the system are evolving at a predictably rapid pace. Although Hayes' suggestions were directed toward the broad scope of drug development, including data management and protocol implementation, it is clear that his warnings also apply specifically to the ethical issues of drug development.

The dissertation is particularly relevant to the movement to harmonize international drug development, since the American system has been adopted as the basic goal for post-1992 Europe. The EEC drug development guidelines, particularly the section dealing with informed consent, are amazingly similar to FDA requirements. This is not so surprising when one considers that informed consent is itself essentially an American development. This points to an even greater need for reflection on American clinical
trial informed consent, as it is difficult to appreciate the need for change when one's system is viewed as the "gold standard" to which others aspire. The dissertation will demonstrate, however, that the American clinical trial informed consent system has limitations that point to a less than optimal process. Thus, in addition to demonstrating the unique contribution that may be made by the theologically trained medical ethicist, this study may also serve to enlighten industry and regulatory officials charged with decision making in such affairs.
Endnotes to Chapter one


The Silent World of Doctor and Patient, p. 60.


Ibid., p. 1229.

Ibid., p. 1230.

A History and Theory of Informed Consent.

Ethics and Regulation of Clinical Research, pp. 95-153.

Ibid., p. 124.

Ibid., p. 126.

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Ibid., pp. 127-140.

The Silent World of Doctor and Patient, p. 1.

Ibid., pp. 1-29.

Ibid., pp. 130-164.


The Patient as Person: Explorations in Medical Ethics, p. 2.
32Ibid., p. 5.

33Ibid., p. 6.

34Ibid., pp. 9-10.


49 Informed Consent: Legal Theory and Clinical Practice, p. 213.


52 Ibid.


59 Ibid., p. 60.

60 Ibid.

61 Ibid., p. 66.


64 Ibid., p. 149.

65 Ibid.

66 Ibid., p. 136.

67 Ibid., p. 139-140.

68 Ibid., p. 140.

69 Ibid., p. 141.


71 Ibid., p. 138.

72 Ibid., pp. 138-139.


74 Ibid.

75 The Modern Theologians: An Introduction to Christian Theology in the Twentieth Century, p. 142.

76 Ibid., p. 143.

77 Systematic Theology, Vol. III, pp. 11-12.

78 Ibid., p. 22.

79 Ibid., p. 298.


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85Ibid.


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CHAPTER TWO

THE ELEMENTS AND SIGNIFICANCE OF THE PARADIGM

Introduction

The notion of clinical trial informed consent as paradigm presupposes a substantial difference between its own concepts and those of informed consent for treatment. The difference is not merely a matter of two variations of a common theme, but is rather a fundamental difference in application of the two models. In Chapter two, I will argue for the existence of a great enough difference in such application to warrant a separate appreciation for clinical trial informed consent. Such a distinction does not negate the conceptual similarities between the two paradigms. Rather, it is the respective use of the models that is important.

Clinical trials and drug regulation

Since this study focuses on a specific sub-category of research informed consent, i.e., that of the clinical testing of new drugs, it will be helpful to briefly introduce the notion of the clinical trial and its
distinctive role within the American drug development process.

In the United States, clinical trials are conducted in a highly regulated environment. The American drug industry was essentially nonregulated before 1938. Previously, federal laws designed to ensure safety and truth in advertising were either ignored or considered to be too difficult to enforce. For instance, the Pure Food and Drugs Act of 1906 was enacted to prohibit false and misleading claims about food and drug products. Referred to as the Wiley Act, after the Agriculture Department's chief food chemist from 1883-1912, this legislation was doomed to failure after a 1911 Supreme Court decision that allowed false or unsubstantiated claims so long as the food or drug package listed the correct ingredients present in the product. Consequently, the Sherley Amendment was passed in 1912, which specifically prohibited false and fraudulent labeling claims. However, this legislation was essentially ineffective, as fraud was difficult to substantiate or prosecute.¹

With the development of sulfanilamide in 1932, it was becoming apparent that a new age in drug discovery was dawning--an age in which science rather than hucksterism was the mainstay of drug research and development. The sulfanilamide derivatives, still known today as the "sulfa
drugs," provided the first effective remedy against a wide range of infectious diseases.

Despite the therapeutic promise held by sulfanilamide, tragedy was soon to strike. Because the powder form of the drug was difficult to measure and left a bad taste, a liquid form of the drug was developed. Only after approximately one hundred people, mostly children, had died as a result of ingesting the new formulation did authorities at the American Medical Association discover that the vehicle used for the dissolution of sulfanilamide was diethylene glycol, a substance that converts to fatal oxalic acid when consumed by humans. Sulfanilamide elixir was never treated in animals, nor were there regulations requiring such testing.²

The Food, Drug, and Cosmetic Act was born out of the sulfanilamide disaster. The act empowered the Food and Drug Administration (FDA), then a constituent agency of the Department of Agriculture, to require warnings on labels, ban dangerous substances, and enforce its regulations. The act also required the manufacturer to submit evidence that a drug was safe, although the FDA was charged with proving that the drug was actually unsafe in order to prevent its marketing.³

Developments between 1938 and 1962, while not facilitating any dramatic changes in the drug approval
process, did provide considerable growth in the technology necessary for new drug development. Antibiotics such as penicillin and streptomycin were discovered, and it appeared as though the United States was indeed entering a new era of medicine. It would take another tragedy to effect any substantive change in the way pharmaceutical compounds were approved for marketing.

A drug with the generic name thalidomide was developed and marketed throughout much of the world in the 1950s. Although never marketed in the United States, the drug was available to more than twelve hundred American physicians as an experimental agent. Marketed in the rest of the world as a hypnotic and sedative, the drug was frequently distributed to pregnant women. Unfortunately, thalidomide was discovered to cause the teratogenic effect of phocomelia, which is characterized by absent or severely underdeveloped limbs.

The manufacturer of thalidomide, Chemie Grunenthal of Germany, withdrew all dosage forms and strengths of the drug when faced with the alarming data about its effects. However, the experimental supplies that had been shipped to American physicians were difficult to track down. Pharmaceutical firms were not required to keep detailed records on the shipment of experimental drugs, and the physicians using such compounds had only to sign a statement
verifying that they were competent to dispense the drug. There were no regulations that patients given thalidomide be informed as to its experimental status.⁴

The thalidomide tragedy was averted in America because of the efforts of FDA staffer Frances Kelsey, who insisted on additional safety data on thalidomide before approving the drug for marketing in the United States.⁵

Essentially because of the widespread concern evoked by the thalidomide tragedy, as well as the desire to prevent such an occurrence in the United States, Senator Estes Kefauver launched a campaign for drug safety and efficacy. In 1962, the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act became law. Passed unanimously, the Kefauver-Harris amendments changed the complexion of the American pharmaceutical industry. Essential features of the legislation were requirements that the efficacy of a drug be established by the manufacturer, and that the Food and Drug Administration be required to act on all drug approval applications. Additional safety parameters were instituted by the Kefauver-Harris amendments, which served to strengthen the safety requirements of the Food, Drug, and Cosmetic Act.⁶

The Kefauver-Harris amendments, which modernized the drug approval process and doubtless saved thousands of
lives, essentially had the effect of placing the responsibility for extensive safety and efficacy testing directly on the pharmaceutical industry. This legislation created the need for well controlled and adequately designed clinical trials. There is no other method of determining a drug's safety and efficacy in human beings than by conducting human clinical trials. Animal research only documents the probability of efficacy, although the same animal research may be relied upon for toxicological and/or safety data.

Clinical trials versus treatment

There are substantive differences between the performance of a clinical trial and the practice of medicine. Levine has described a basic difference as being the separate interests represented in the two scenarios. In a clinical trial, the research is designed to be utilitarian. That is, one hopes to generalize the findings of a clinical trial to society at large, or at least those members of society who are afflicted with the disease being studied. Thus the interests of persons other than the subject are the primary reasons for conducting the trial in the first place. In medical treatment, however, the interest of the individual patient is paramount. A therapeutic relationship is negotiated between the physician
and the patient—-one that aims to benefit the patient, with no thought given to any broader societal interests.  

Appelbaum similarly sees the primary difference between treatment and research to be one of conflicts of interest. This divergence of interests is rooted in the basic difference between the production of general knowledge and the promotion of individual health, as "(s)teps taken to protect the generalizability of the data may conflict with the maximization of benefit to the individual subject."

The priorities of different interests in clinical trials and in treatment cannot be denied. The research subject is not a patient in any true sense of the word. Once an individual assumes "subject" status, he or she loses the right, within the context of the clinical trial protocol, to the more traditional physician-patient relationship. The research protocol must be followed, and there is generally little room for variation insofar as individual situations are concerned. Of course, an exception to the rigidity of the protocol and the resultant loss of patient status is the situation in which a serious adverse event or other untoward occurrence precludes the subject’s continued participation in the research project. Should this occur, the subject is immediately dropped from the trial, and resumes "patient" status. A similar situation is the use of statistical "stopping rules", which
are designed to stop a trial before completion if newly analyzed safety or efficacy data warrant such action. However, these scenarios do not negate the fact that, while enrolled in the protocol itself, the clinical trial subject has no "patient" status.

The conflict of interest theory espoused by Levine and Appelbaum, while plausible, is only applicable at the operational level. That is, one can clearly discern the conflict of priorities in clinical trials and practice when one focuses on the direct physician-patient or investigator-subject relationship. Less clear are the differences between the applications of informed consent in the two scenarios—differences that may be fully appreciated only within an appreciation of clinical trial informed consent as a fundamentally different paradigm from informed consent for treatment.

In Chapter one I sketched the categories of the new paradigm. I will now move to a more detailed explication of these categories and their significance.

Recruitment as paradigm category

The success of a clinical trial depends largely upon the investigator’s ability to recruit an adequate number of subjects into the project. Unfortunately, the recruitment
of clinical trial subjects is oftentimes the most frustrating experience of an investigator's career. Investigators, particularly those that are relatively inexperienced, tend to be overly optimistic about their ability to recruit clinical trial subjects—an optimism that is fueled in part by sketchy initial information given to the investigator by the sponsor of the trial. Frequently, an investigator is approached by a research representative of the sponsor, usually a pharmaceutical company, and asked if he or she wishes to participate in a multi-center trial within the investigator's specialty. The title of the trial gives the investigator a general indication as to the specifics of the study and what is expected. For example, a trial entitled "A Multiple Dose Comparison of XYZ with its Components in a Twelve-Week, Parallel Study in Adults with Chronic Obstructive Pulmonary Disease (COPD)" would obviously require the investigator to recruit pulmonary subjects. Within the body of the protocol, the investigator is told how many subjects each center is expected to complete. A typical multi-center trial involves twenty to thirty subjects per center. This appears to be an easily achievable goal for the busy investigator, whether institutionally based or in private practice. For example, the University of Texas Medical Branch at Galveston currently has a population of approximately twenty five hundred chronic obstructive pulmonary patients followed in
its Division of Pulmonary Medicine. Thus investigators all too often assume, based upon the number of subjects needed and the available number of patients with the disease in question, that recruitment of clinical trial subjects is the least of their worries.

The awakening for the investigator comes with the realization that the protocol requires not just twenty or thirty subjects who are afflicted with the disease in question, but more specifically twenty or thirty subjects who meet the rather rigid inclusion/exclusion criteria for the clinical trial. In the above referenced protocol, for example, one finds the following inclusion/exclusion criteria:

Inclusion Criteria

1. All subjects must have a diagnosis of chronic obstructive pulmonary disease according to the following criteria: Subjects must have relatively stable, moderately severe airway obstruction with an FEV1 of less than 65% of predicted normal and FEV1 of less than 70% of FVC.

2. Subjects must have a history of being prescribed at least two therapeutic agents, by a physician, for use on a regular basis for control of their chronic obstructive pulmonary disease symptoms during the three-month period immediately preceding consideration for entry into this study.

3. Male or female subjects forty years of age or older.

4. Subjects must have a smoking history of more than ten pack-years. A pack-year is defined as
the equivalent of smoking one pack of cigarettes per day for a year.

5. Subjects must be able to perform pulmonary function tests, peak flow measurements, and maintain records as required in the protocol.

Exclusion Criteria

1. Subjects with significant diseases other than chronic obstructive pulmonary disease will be excluded. A significant disease is defined as a disease which in the opinion of the investigator may either put the subject at risk because of participation in the study or a disease which may influence the results of the study or the subject's ability to participate in the study.

2. Subjects with clinically significant abnormal baseline CBC, SMA-12 or urinalysis if the abnormality defines a disease listed as an exclusion criteria.

3. All subjects with SGOT of greater than 80 IU/L, bilirubin greater than 2 mg/dl, or creatinine greater than 2 mg/dl will be excluded regardless of the clinical condition.

4. Subjects with a one-year history of myocardial infarction.

5. Subjects with a history of cancer within the past five years.

6. Subjects with any viral infection or febrile illness within the last month.

7. Subjects with known symptomatic prostatic hypertrophy or bladder neck obstruction.

8. Subjects with glaucoma.¹²

When considering these inclusion/exclusion criteria, the investigator quickly realizes that up to 90% of all patients from the available patient pool fail to qualify for
a given clinical trial. Thus the investigator quickly discovers that an attitude of "merely signing patients up as subjects" is insufficient, and that more aggressive recruitment efforts must be initiated.

Clinical trial subjects are recruited from a variety of sources. For Phase I studies, also known as "first time in man" trials, subjects must be young healthy males who can remain in a clinical pharmacology unit for up to twenty-eight days. For this reason, the unemployed are frequently targeted for recruitment in such trials. At some centers, medical students are recruited for very short Phase I studies.

Many investigators advertise for clinical trial subjects. This is true for both "normal volunteer" (Phase I) studies as well as for "patient" studies (Phases II-IV). If one peruses the campus bulletin boards of any medical school or large medical center in the United States, one will usually discover advertisements for subjects needed for trials ranging from "first time in man" studies to efficacy trials on new drugs designed to treat hay fever. At the other end of the spectrum, one may find physician-investigators actively recruiting potential subjects from their own practices. In between the two extremes, one frequently finds potential subjects being recruited by their own physicians for clinical trials conducted by someone
else. This practice is especially prevalent in the medical school and teaching hospital environment.

The reality of clinical trial recruitment helps demonstrate the necessary distinction that must be made between the process of informed consent and the actual signing of the consent form. All too often, the obtaining of a signed consent form is viewed as the "ethical be-all and end-all of research with human subjects."\(^{15}\) Regardless of the method of recruitment, however, the reality of the transaction between the investigator and the subject points to informed consent as an ethical process. If an individual answers a newspaper advertisement for a new bronchodilator study, the process of informed consent begins well before he or she meets the investigator. The advertisement itself contains crucial information concerning the trial, or at minimum should state that persons are being recruited for a research protocol. Similarly, the subject recruited by one physician for a trial being conducted by another physician-investigator begins the informed consent process before meeting the person actually conducting the trial. Even in the case of a subject being recruited by an investigator out of his or her own practice, one may still find that the investigator is not the first contact for the potential subject. Almost all investigators employ "study
coordinators" who recruit subjects and handle the day-to-day responsibilities of the clinical trial.

The significance of the notion of recruitment for clinical trials lies in the fact that the process of informed consent thus begins much earlier than in the treatment model. Rather than in the physician's office or at the hospital bedside, clinical trial informed consent as process begins at the moment the potential subject becomes aware of the trial. The significance of this distinction will become even more apparent in Chapter three's critical examination of clinical trial informed consent practices.

Potential subjects as outsiders

Regardless of the recruitment method or the source from which potential subjects are recruited into a clinical trial, these individuals do not possess a "medical identity" within the research project itself. This supposition is based on the fact that, at least for the purpose and duration of the trial, the subject is a means to a larger end. The clinical trial is designed to answer a question—an answer that can only be obtained by pooling the research results. The subject's identity in such a scenario is basically reduced to that of a "data set," as indelicate as this may appear. Even subjects who are recruited from the investigator's practice, i.e., subjects who are otherwise
patients of the physician-investigator, lose most of their patient identity in the trial due to the rigid confines of the protocol. Quite simply, there is little room for patient care in clinical trials, as any physician-patient therapeutic negotiations are factored out by the requirements of the protocol.

A critical distinction must be made at this juncture between care for the subject and the overall notion of patient care. The former refers to notions such as spending time with and paying close attention to the subject, whereas patient care may be used to describe the relationship that exists between the physician as healer and the sick patient. If a treatment regimen is not working for a patient, the physician may make appropriate adjustments in medication or dosages, or may recommend other treatment such as surgery. On the other hand, the choices in a clinical trial are essentially to either follow a relatively inflexible protocol or drop the subject out of the study altogether. But this does not necessarily mean that the research subject is relegated to second class status. Rather, this lack of flexibility in the protocol only points to the fact that, again, the purpose of a clinical trial is the generation of data.

Louis Lasagna has pointed out that research subjects may well in fact be "cared for" in a better manner than
patients.\textsuperscript{16} Interestingly, Lasagna bases this assertion not entirely on the notion that more time is spent with study subjects than with regular patients, but also on the fact that the required restraints of the research protocol insulate the subject from the baleful results of overly aggressive treatment. Iatrogenic mishaps aside, Lasagna’s thesis gains credibility when one considers that long waits for appointments or investigators being late for scheduled visits, etc., are almost unheard of in clinical trials. The credibility of the data demands strict adherence to protocol requirements—an adherence that applies equally to investigators and subjects.

The difference between research and treatment, and the corresponding effect upon informed consent practices, may point to the outsider role in a much different way. James Sellers has suggested that informed consent’s central priority of autonomy, or free choice by the individual, invites an examination of the relationship between justice and informed consent. Looking at the civil rights movement and the American tradition of justice, Sellers concludes that informed consent is the medical ethics equivalent of liberty.\textsuperscript{17} However, liberty as found in medical ethics is quite different from the liberty gained by blacks in the civil rights movement. In the case of the civil rights movement, liberty granting contingencies such as the right
to vote and use public accommodations preceded zero-sum game activities such as competing for specific jobs. In medicine, however, the liberty represented by informed consent resides within an already existing realm of medical practice. That is, informed consent is something to be enjoyed by one already in the system of medical care, and therefore is not a "portal" of entry into the medical scheme.\(^8\)

Sellers' argument, while persuasive, appears to point exclusively to the notion of informed consent for medical treatment:

Informed consent is a right embedded within what remains a privilege rather than a right in and of itself. It does not point the way to further goods but is rather a benefit for those who have already gained the status of patient.\(^9\)

Sellers' position would have to be substantially modified to apply it to the clinical trial scenario. In fact, clinical trial informed consent is a portal of entry into the system, since no previous patient status needs to be attained. When a person is being considered for entry into a clinical trial, it matters not at all where he or she falls within the medical establishment qua system. Insurance coverage or demonstration of the ability to pay are foreign concepts in clinical trials. All that matters is that the potential subject meets the inclusion/exclusion
criteria for the trial. In this regard, clinical trial informed consent is arguably closer to the notion of justice than are vehicles for entry into medical treatment systems. For the outsider, or Sellers' "have-nots," clinical trial informed consent may well be an instrument of justice.

Human experimentation

The third major difference between informed consent for clinical trials and for treatment is that clinical trials exemplify human experimentation. The clinical trial is designed to provide answers to scientific questions, and must rely upon the use of human subjects for collection of the necessary data. However, if it is not altogether obvious that clinical trials are exemplars of human experimentation, the responsibility could lie with those who insist on categorizing trials as "therapeutic" or "non-therapeutic." Such an approach, while perhaps useful insofar as distinguishing between basic safety studies and those designed to determine efficacy of the drug in sick persons, nonetheless tends to blur the relationship between clinical research and human experimentation.

The literature is replete with references to the difference between "research volunteers" and "research patients." Lasagna has suggested that the volunteer is "truly an experimental subject," whereas the "research
patient" may indeed derive some benefit from participation in the project, and hence is a different category of subject. Lasagna goes so far as to suggest that the two types of research subjects be treated differently, although he does not specifically address how this should be done.\textsuperscript{20}

Lasagna's separation of "volunteer" and "patient" research does not merely reflect the complexity of modern clinical trials. The Declaration of Helsinki clearly distinguishes between "clinical research combined with patient care" and "non-therapeutic clinical research."\textsuperscript{21} In the case of "patient" research, informed consent should be obtained "if at all possible, consistent with patient psychology."\textsuperscript{22} This phrase has led Appelbaum to suggest that, if following only the Declaration of Helsinki, researchers have considerable latitude in determining whether or not informed consent is necessary in a given case.\textsuperscript{23}

Henry K. Beecher's seminal research on ethics and clinical research similarly distinguishes between studies on "patient volunteers and normal subjects" and "experimentation on a patient not for his benefit but for that, at least in theory, of patients in general."\textsuperscript{24} While Beecher claims to concentrate only on the latter category, he does not explain how research on a normal subject could possibly be of benefit to that subject.
Again, there are practical reasons to distinguish between various types of clinical trials. Terms such as "therapeutic", "non-therapeutic", "patient studies," and "volunteer studies" serve to clarify and categorize the nature and purpose of the trial. However, such categorization also may blur the distinction between human experimentation and the frequent trial and error approach to clinical care. A "therapeutic" Phase III clinical trial, for example, may compare the efficacy of an experimental drug to a well known and adequately established agent. Since earlier Phase II trials have already suggested that the experimental drug is efficacious, the primary objective of the Phase III trials is to provide an adequate number of subjects for a valid statistical analysis. In both groups of the trial, which interestingly are referred to in statistical jargon as "treatment groups," the subjects are receiving an active substance for treatment of their disease. In this regard, the term "therapeutic" is misleading, as it points only to the fact that the subjects are receiving either an experimental or proven "therapeutic" substance. However, to imply that the trial is therapeutic for the individual research subject represents a fundamental misunderstanding of the clinical research process. The so-called therapeutic nature of some clinical trials, as well as any distinction between normal volunteers and patient-
subjects, in no way lessens the experimental nature of the research project. That is, the status of experiment should not be granted by reliance upon criteria such as the subject’s health status or the fact that he or she may obtain some benefit from participation in the research.

What then determines the experimental nature of clinical trials? The key element is the protocol, or scientific plan for the project. It is this document, usually twenty to thirty pages in length, that defines the boundaries of the relationship between the investigator and the subject. These boundaries, and their non-negotiable status, establish limits as to what may transpire between the parties. Investigators simply do not have the same options available to them as do physicians who are treating patients. In a clinical trial, if the drug is not working, the only options are to either increase the dose at the next stage where this is allowable, or to terminate the subject’s participation. The investigator may not, as in treatment, merely add other drugs or introduce other interventions.

The interference that the protocol introduces to the treatment decision process is the major difference between research and treatment. In this regard, all clinical trials are exemplars of human experimentation. The integrity of clinical trial informed consent is compromised to the degree that this fact is not appreciated.
The significance of the paradigm

The suggestion that there exists a separate paradigm for clinical trial informed consent is, let us hope, of more than academic interest. There are well-documented deficiencies in informed consent practices in the United States.25 The exploration of any such deficiencies in the realm of clinical research is hindered by approaches that rely upon the assumption that clinical trial informed consent is basically a variation of informed consent for treatment. The paradigm is thus not only of interest conceptually, but is pivotal insofar as suggestions for change are concerned.

Criticisms of informed consent

There is no shortage of criticisms of informed consent, both in regard to treatment and research.

Barrie R. Cassileth has examined the reasons that patients are frequently unable to recall pertinent information about pending medical treatment or surgery for which they had ostensibly given informed consent. In his study, Cassileth and his colleagues found that of 200 cancer patients, only 60% understood the basics of the pending procedure, and only 55% could correctly recall any major
risks—all of this only one day after signing the consent form.

Cassileth draws the conclusion that the patient's failure to recall this basic information indicates that medical information is too difficult for these persons to understand. This claim has also been advanced by M.D. Kirby. Such a conclusion relies heavily upon the transaction model of consent, i.e., that of the immediate consent conversation and signing of the form. This is understandable when one notes that Cassileth's study is basically a consent form study, rather than an examination of consent per se. However, Cassileth is correct in pointing out that informed consent is frequently not valid in practice, as competent persons who cannot recall even the most basic information about the procedure consented to the day before cannot be said to have adequately understood it in the first place. Unfortunately, Cassileth offers no prescriptive advice for remedying this situation.

William A. Silverman has offered a comparison of the practice of informed consent in medical treatment and clinical trials in America. Silverman describes the transition from early beneficence-based models to the distinctively American notion of informed consent as the recognition of and respect for the autonomy of the patient or research subject. Silverman also calls attention to the
fact that treatment informed consent is oftentimes at best a malpractice hedge for physicians, or with higher motives, a legitimate exercise of ethically appropriate behavior. At any rate, treatment informed consent is something that physicians are *exorted* to obtain. On the other hand, because of federal guidelines on the conduct of clinical trials, research informed consent is something that clinical investigators are always *compelled* to obtain. Neither motivation has led to any assurance that the spirit of valid informed consent has been successfully addressed, leading Silverman to speculate that one cannot devise informed consent practices that satisfy, in full, the competing moral imperatives of respect for autonomy, concern for beneficence with emphasis on the value of health, and a vigil for justice.  

Silverman does not propose a specific solution to the problem he identifies, other than the general suggestion that a method be found "that would strike a realistic balance among competing interests." 

In structuring his discussion around the reality of two different consent scenarios, i.e., treatment and research, Silverman has explicated a duality in the overall consent system that is frequently overlooked. Informed consent for treatment is not synonymous with informed consent for research, and the difference is more significant than any
disparity between legal requirements of research informed consent and ethical, or even self-serving, requirements for treatment informed consent. The difference lies in the two different informed consent processes. Persons enter clinical trials for reasons other than to obtain medical treatment, although one may argue that there is frequently a strong expectation of treatment on the part of clinical trial subjects.\textsuperscript{31} Appelbaum, for instance, has described a phenomenon called the "therapeutic misconception" of clinical trial subjects:

...subjects are likely to extrapolate from the clinical setting, assuming that research procedures are intended to benefit them or at the least not to cause them harm.\textsuperscript{32}

The serious observer must take Appelbaum's notion of "therapeutic misconception" into account, although it is based upon only four psychiatric studies.\textsuperscript{33} The physician-patient relationship is for many individuals one of implicit trust in the supposition that the physician's motives are always in the best interest of the patient. Unfortunately, the notion of "best interest of the patient" all too often undermines the recognition of the patient or subject as autonomous being.

Clinical trial informed consent is clearly dependent upon the facilitation of communication between the
investigator and the research subject. David J. Roy has advanced the argument for communication in research:

Some scientists—who knows how many?—still look upon "obtaining informed consent" as a legally imposed and obstructive ritual. They have to "get" the patient's or the subject's consent. They see it as something they need for their research. Obtaining written consent on a consent form offers little evidence that careful communication designed to maximize the patient's or subject's understanding has in fact taken place.34

Roy's observations clearly point toward the need for an informed consent process that relies heavily upon proper communication. The implementation of such a valid research informed consent process may well be undermined by the legalistic and regulatory settings of clinical trial informed consent, i.e., the viewing of informed consent as a documentation requirement to be obtained from the potential subject.

Beauchamp has provided a concise but insightful understanding of the problem of viewing informed consent in legalistic or regulatory terms, arguing that:

...the central problems about informed consent are issues of communication rather than the abstract and disembodied issues about proper legal standards of disclosure that have so long dominated the subject literature.35

Beauchamp further explains that informed consent regulations have been derived from the notion of protecting
patients and research subjects from "harm, exploitation, and injustice." The issue of patient autonomy, so emphasized in contemporary discussions in medical ethics, played if anything a secondary role in the initial formulation of informed consent guidelines in the United States. Although autonomy is now addressed in informed consent policies and procedures, it is also clear that in practice the patient's or potential subject's autonomy is relegated to a second-order status even by physicians and investigators whose paternalism is heavily influenced by beneficence. In fact, it is perhaps these individuals who violate the process of informed consent with the most regularity.

Beauchamp's concerns may be translated into the clinical trial setting by considering the case of the poor, essentially illiterate person being recruited for a clinical trial. One can justifiably argue that even if the informed consent document is written, as required by federal regulations, in language understandable to the subject, there is little evidence that he or she will understand or necessarily read the document. This is particularly true in the case of a subject who trusts that the investigator has his or her best interest at heart--a common assumption made of physicians in the American culture, although perhaps not now as prevalent as previously.
"Good will," or taking what is best for the potential subject to heart, even by the best intentioned investigator, does not guarantee valid informed consent. In fact, to the degree that such an attitude excludes the potential subject from autonomous decision making, it is actually contradictory to the notion of a valid informed consent.

One cannot rationally dispute the fact that the beneficence model of medical treatment and research has brought much ultimate good both to the individual research subject and to society at large. Nor can one logically claim that beneficence has no role in such affairs. However, it seems clear that a reliance upon beneficent motives, however well intentioned, may lead to paternalistic behavior that is in the best interest of neither the potential research subject nor society at large.

In the example of informed consent, it would appear that biases toward paternalistic behavior on the part of investigators are related to the degree of deemphasis of subject autonomy that is present. That is, the less one is concerned with the potential subject's right to make a truly autonomous decision, the more likely one is to exhibit paternalistic behavior.

The reliance upon beneficent motives in informed consent, and the corresponding deemphasis on the right of
potential subjects to an autonomous decision, may easily be overlooked in the informed consent process. After all, one could argue, does not the institutional review process prevent any overriding of the potential subject’s autonomy? Does not Institutional Review Board (IRB) approval serve to assure the existence of valid informed consent in a clinical trial?

Questions such as these serve to provide a framework for an exploration of the differences between informed consent theory and the practice of obtaining informed consent documentation. Roy describes the difference in this manner:

Some investigators...speak and behave as though obtaining consent is the ethical be-all and end-all of research with human subjects. The attitude frequently seems to be: if only I can get that consent, I can get on with what is really important, my research.  

This attitude, which may indeed be based upon beneficent motives, serves to undermine the notion of informed consent as process—a notion that serves as a basic premise of the clinical trial informed consent paradigm of recruitment of outsiders into the realm of human experimentation.

In addition to these general criticisms of informed consent, there are specific limitations to be found within
the categories of the clinical trial informed consent paradigm. For the thesis to be valid, these categories, along with their limitations, must possess an affinity for the love and justice categories of Ramsey and Rawls. Chapter three will focus on an explication of these correlative relationships.
Endnotes to Chapter two

1Boehringer Ingelheim Pharmaceuticals, Inc., internal correspondence. Derived from a presentation by A. Segretti. Undated.


3Ibid., p. 23.

4Ibid., pp. 21, 24, 25-27.

5Ibid., pp. 25-26.

6Ibid., pp. 21-29.


9Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, Fundamentals of Clinical Trials (Boston: John Wright, 1983), pp. 100-111.

10Protocol on file, Boehringer Ingelheim Pharmaceuticals, Inc.

11Personal communication with Juan Nadal, M.D.

12Protocol on file, Boehringer Ingelheim Pharmaceuticals, Inc.

13Personal communication with Charles Serby, M.D.


18 Ibid., p. 50.

19 Ibid.


22 Ibid.


26 Ibid.


29 Ibid., p. 6.

30 Ibid., p. 10.


34 Ibid., p. 24.


37 "Informed Consent: Obligations and Limits," p. 27.
CHAPTER THREE

ANALYSIS OF THE PARADIGM

Introduction

Correcting deficiencies in clinical trial informed consent has been explored by several authors.¹⁻³ Deborah R. Norris and Michael R. Phillips have suggested that the traditional clinical trial informed consent transaction of a verbal exchange between the investigator and potential subject, followed by the signing of the consent form, may be successfully supplemented with audiovisual aids. Specifically, Norris and Phillips demonstrate that instructive videotapes may enhance a potential subject's understanding of the protocol. The benefit from such enhancement is not limited solely to the informed consent transaction, but also helps insure better compliance by the subject of the research protocol.⁴ Thus one can expect not only a more valid consent, but better quality research data as well.

Levine suggests that the element of time is a critical factor in informed consent negotiations. This applies to the amount of time the potential subject is allowed for
deciding whether to participate in the clinical trial, as well as the actual temporal relationship between the transaction and other aspects of the study. Potential subjects should be given adequate time to consider their consent and to consult with trusted others. A similar point is made by Kirby, who suggests that potential subjects should be provided with relevant information that they can "take away and consider at leisure." Further, Levine asserts that if informed consent has been obtained well in advance of the beginning of the research project, the potential subject should be reminded of his or her right to withdraw consent before the project actually begins.

An example of this type of consent transaction is an analgesic study performed in an obstetrical practice. Potential subjects may be recruited months before their expected delivery dates. This is certainly preferable to being recruited after labor begins. However, numerous factors could cause the potential subject to change her mind in the interim. There must be a method of respecting this new decision.

These suggestions focus on specific issues of the informed consent transaction between the investigator and the potential subject. These voices, while instructive and useful in a practical sense, fail to address the deeper issues that are present within the paradigm categories of
recruitment, outsider, and human experimentation. This is understandable because of the generally accepted view of informed consent as "something to obtain." However, the existence of the clinical trial informed consent paradigm, i.e., the notion of the recruitment of outsiders into the realm of human experimentation, begs us to look deeper than the transaction itself—a transaction that may all too often appear to be an isolated, singular event. This paradigm, which was described in Chapter two, must be analyzed from the perspective of identifying its underlying concepts and their relationship to a valid consent process. Only in this fashion may we attempt to see what lies below the transactional surface of clinical trial informed consent. Further, such an examination allows for the demonstration of a correlative relationship between the paradigm categories and the thought of Ramsey and Rawls.

Recruitment

In Chapter two I explicated the notion of clinical trial recruitment and its critical role in the success of a given trial. As was discussed, recruitment difficulties are numerous. The difficulties an investigator faces can be addressed in logistically related terms, such as manpower deployment, increased advertising, more aggressive recruiting, etc. 7-11
Potential clinical research subjects do not generally approach investigators and express their desire to be enrolled in a clinical trial.\textsuperscript{12} Rather, the investigators must rely upon the notion of recruitment to acquire qualified subjects. Recruiting of qualified subjects is one of the most critical tasks confronting the clinical investigator.\textsuperscript{13,14} The success of a given trial is viewed as being a matter of numbers—both the number of subjects recruited and the number who ultimately successfully complete the protocol.

As outlined in Chapter two, clinical research subjects may come from a variety of sources. The unemployed and indigent are frequently recruited for Phase I, or "first time in man" studies. Students are also frequently recruited, as they represent a class of individuals with a considerable amount of discretionary time on their hands—a frequent prerequisite for clinical trial participation. Also, investigators frequently recruit for clinical trials from within their own practices, or from the practices of colleagues.

James M. Swinehart, in what must be described as a rather aggressive stance toward subject recruitment, suggests the implementation of a "Marketing Plan" for purposes of bringing subjects into the clinical trial. Such a marketing scheme would include a computerized compilation
of potential subjects to be contacted by the study coordinator. Swinehart's lists are derived from disease support organizations, hospital publications, newcomers to town, and even church groups. The study coordinator can then approach persons identified in such a fashion, and does not have to rely upon potential subjects noticing an advertisement. Interestingly, Swinehart claims that such a marketing plan has a high level of success in baldness and smoking cessation trials, but does not work as well for strep throat studies. The acute nature of many disorders presumably prevents too heavy a reliance upon such advance recruiting.

Similarly, Mary Ann F. Kirkpatrick suggests that, to optimize subject recruitment, investigators should be aware of what motivates persons to participate in clinical trials. Such motivational factors range from the stipend provided by the sponsoring pharmaceutical company to the knowledge that one is benefitting medical science.

Although such activity may certainly help generate a higher enrollment in a given clinical trial, a too narrow focus on these remedial measures may well ignore the obvious ethical ramifications of clinical trial recruitment. One must be mindful of the fact that clinical trial recruitment is essentially the "bringing in" of human subjects into the realm of research.
This perspective, i.e., focusing upon the recruitment of human beings rather than upon the relative efficiency of recruitment activity, points to the notion of fairness in the clinical trial informed consent process. One can think of the logistics of recruitment in administrative terms. However, the persuasive scenario of an investigator suggesting that a person may wish to be a research subject requires that fair practices be implemented.

Others have commented upon the notion of fairness in clinical trials.\textsuperscript{18-22} Observations range from the coercive nature of clinical trials\textsuperscript{23} to actual suggestions as to who should be clinical trial subjects.\textsuperscript{24} Grant Gillett's notion of the coercive nature of clinical research is particularly disturbing when one considers that the medical community itself, due in part to a lack of effective communication between parties, is inherently coercive.\textsuperscript{25,26}

The processes of coercion and unfairness do not apply exclusively to potential subjects "outside" the medical system. Ingelfinger has noted:

Incapacitated and hospitalized because of the illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, he is far from exercising a free power of choice when the person to whom he anchors all hopes asks "Say, you wouldn't mind, would you, if you joined some of the other patients on the floor and helped us carry out some very important research we are doing?" When 'informed consent'
is obtained, it is not the student, the destitute bum, or the prisoner to whom, by virtue of his condition, the thumb screws of coercion are most relentlessly applied; it is the most used and useful of all experimental subjects, the patient with disease. 27

In similar fashion, patient-subjects have been described as "the most captive" of trial subjects, 28 and may be particularly vulnerable when suffering from long standing, refractory illnesses. 29

If subjects and potential subjects are not treated fairly in the clinical trial informed consent process, one can expect the integrity of the paradigm category of recruitment to be compromised. Examples of unfair conduct in the clinical trial informed consent scheme could be, for instance, a grossly unequal distribution of the burdens of research onto the less advantaged members of society. However, it is clear that as long as clinical trial participation is voluntary, an equal distribution of research benefits and burdens is an unrealistic expectation. Conscription into clinical trials could serve to insure that the more advantaged, and hence more likely to be positioned to profit from the rewards of research, were properly represented in the burdensome and risky realm of the clinical trial subject. This, however, is an unlikely scenario in our society.
A more likely fairness issue in the clinical trial informed consent paradigm category of recruitment is that of fairness in the broad background of research informed consent and the institutions in which it is obtained. One must not overlook the fact that clinical trial informed consent is first and foremost an institutional issue. Clinical trial informed consent does not occur within a vacuum in which only the potential subject and the investigator participate. The institutions involved in the paradigm can be of mortar and brick, such as medical schools and hospitals, and also can be notional, such as the practice of medicine and the role of the physician in society, or of medical research itself. Such institutions must be fairly based or else not only the distribution of research burdens will be overwhelmingly skewed, but also the day-to-day implementation of the clinical trial informed consent transaction will also be affected. It is not overimaginative to visualize the following example as instructive for this point:

A less advantaged minority individual has hypertension that, for economic reasons and the lack of available health care, is largely untreated. The only medical facility readily accessible to such an individual is the local public university hospital, as the patient either
has no health insurance or, if insured, cannot pay the deductible. Unfortunately, clinic visits at the local university, even with an appointment, can take the better part of a day to complete. At each stop along the way, laboratory, x-ray, patient counseling, etc., there is another long line to endure. The indignity of waiting is bad enough, but our representative patient is an hourly wage employee in a labor pool and receives no pay for this day spent at the clinic. Once he does get to see a physician, it is more often than not a resident in training. While competent to treat and manage most routine cases such as hypertension, the resident is often so busy as to be able to afford only a little time for each individual patient. Of course, the same holds true for practically any medical professional with whom our patient comes in contact. The time available is barely enough to manage the patient’s condition; to actually listen to and give the patient any degree of attention as a human sufferer is almost impossible, even for the best intentioned health care provider. Then, once a diagnosis is made, the patient receives virtually no compliance counseling, other than to "take the medication as directed." There is little chance
for meaningful dialogue between the patient and any of the persons with whom he comes in contact. Then, of course, the resident physician must prescribe a drug that is on the state's Medicaid formulary, or else go through a laundry list of bureaucratic maneuvering in order to prescribe a non-formulary drug. As before, the physician simply does not have time for such considerations. So our patient does not receive, as he would in the private sector, the treatment that his physician feels is the best, but rather gets whatever the state, under ever-tightening budgetary restraints, is willing to pay.

However, one day our patient receives a telephone call from a "study coordinator" suggesting that he consider participating in an upcoming clinical trial at this same university clinic. The purpose of the study is to test the effectiveness and safety of a new medication for the treatment of hypertension. If the patient, who is now more correctly referred to as a "potential subject," agrees to participate, he can expect a thorough examination by the head of the section, followed by lengthy feedback and counseling concerning his health status. A
complete battery of examinations, e.g., blood tests and x-rays, would be performed. The individual, who at this stage would have achieved "subject" status, would be scheduled for bi-weekly clinic visits with this same full professor of medicine. In the course of the visits, there would be adequate time for the subject to discuss any and all concerns with the professor, who, because the trial requires that he assess "quality of life" issues, must be available for such discourse. Clinic appointments are scheduled well in advance, and because they involve the agenda of a professor and section head, rather than that of a harried resident in training, are almost always on time. Further, the coordinator states that the potential subject, if he agrees to participate, will be paid a stipend of $300. Of course, the potential subject will not be charged for any professional services, as the pharmaceutical company sponsoring the trial provides a grant that covers all costs.

It is clear why clinical trial subjects may justifiably be referred to as receiving "preferred status." With this scenario in mind, is it any wonder why the person in this example would lean toward participation in the research
project? One must appreciate that during the initial telephone call from the study coordinator, the potential subject is only supposed to be made aware of the trial and what to expect in the event of his participation. He will than come into the clinic for evaluation, i.e., whether or not inclusion and exclusion criteria are met. At this point also comes the formal informed consent transaction, i.e., the explanation, reading, and signing of the consent form. However, what may easily be overlooked at this time is that the informed consent process actually began when the study coordinator first called the patient. This is, after all, the first step in the recruitment of the outsider into the realm of human experimentation—a step that should be clearly defined as such.

Can one really expect that the potential subject in such a scenario will be totally objective in weighing the risks and benefits for study participation? In fact, is it even likely that a decision to participate in the trial has not already been made by the potential subject before even coming to the clinic for the preliminary visit? Again, the key but easily overlooked issue here is that the informed consent process began with the telephone contact. Reflection on this scenario points to the existence of at least three institutional forces at work. First, there is the issue of health care for the poor. Of course, this one
issue contains several smaller sub-issues, such as access and affordability. Second, there is the institutional structure of the medical school clinic to be reckoned with. Such a system is inherently coercive to begin with,\textsuperscript{32,33} but especially so in the case of the underprivileged. Third, separate from the institution of the hospital is the actual provider-patient relationship. When choices are limited, as they frequently are in publicly funded university hospitals, the patient is quickly cast into the less favorable position.\textsuperscript{34} These institutional forces confirm that fairness issues are at work immediately in the clinical trial informed consent process, and are not limited strictly to the distribution of research burdens or the fairness of formal disclosure via the official informed consent documents.

Outsiders

In Chapter two I outlined the significance of the notion of "outsiders" as the prevalent status of the potential clinical trial subject. Essentially, most clinical trial subjects are stripped of their "medical identity" when they enroll in the research project. The relationship between the investigator and the potential subject is thus considerably different from that between the physician and patient. In the physician-patient
interaction, for example, there is immediately established a relationship between the physician qua caregiver and the sick patient. Such a relationship has invited analysis in its own right, but suffice it to say here that there is a recognized, if at times intangible linkage between the two parties. In the clinical trial setting, however, this relationality of care simply does not exist.

The relationship between the investigator and the clinical trial subject is, at best, transient and temporary. The potential subject may well have never seen the investigator, and further may well expect not to see the investigator at any time in the future. Of course, this transient and temporary relationship may also occur within the treatment model, e.g., in Health Maintenance Organizations. However, patients in such pre-paid plans do possess a "medical identity" that is lacking for the potential clinical trial subject. Even if the potential subject is a patient in the true sense of the word, frequently he or she is a patient within another medical system. For example, a person who is a patient within a private clinic system could presumably respond to an advertisement for a clinical trial being conducted at a local medical school or university hospital. In this case, the potential subject would be a patient within the global medical system, but not within the specific system in which
the clinical trial is being conducted. The distinction is significant, as it is the one-to-one relationality between the investigator and the potential subject that in large part determines the legitimacy and integrity of the clinical trial informed consent process and transaction.

A further problem encountered within the notion of potential subjects as "outsiders" is the use of the consent form itself. All too often, the consent form is viewed as the primary method of bringing the outsiders into the trial. Unfortunately, written informed consent as method is fraught with problems.\textsuperscript{36-41} Gillett, for instance, describes many consent forms as "vague" and "uninformative."\textsuperscript{42} Levine, in a more cynical mood, characterizes clinical trial consent forms as "instrument(s) designed to protect the interests of investigators and their institutions, and to defend them against civil or criminal liability."\textsuperscript{43} Similarly, James M. Vaccarino notes the temptation to confuse informed consent with the documentation of informed consent, referring to the confusion of the two as "the most egregious misconception by physicians concerning informed consent."\textsuperscript{44}

In part because of the nature of the consent form, and the institutional system's insistence and priority on the documentation of informed consent, clinical trial informed consent can easily become more regulatory than ethical. Once this occurs, the consent form all too easily becomes
what Sellers describes as "...a formality, a government requirement, a review board digression." In this situation, i.e., the use of the consent form as a method of bringing in the outsider, it is clear that the focus shifts away from the ethical meaning of clinical trial informed consent and toward its regulatory and institutional components.

Further, and quite possibly most important, the use of the consent form is heavily influenced by the investigator's attitude toward the potential subject as stranger. That is, the investigator may all too easily look at the consent form as the primary communication tool for his or her negotiation with this previously unknown person from outside the immediate medical system. Since the relationship between the investigator and the potential subject, or even the actual subject, is transient and temporary, there can be a strong inclination to ignore or postpone communication. Rather than the consent form being utilized as an instrument designed to guide the negotiation with the potential subject, all too often the consent form is utilized strictly as a method of informing the potential subject—a method that seemingly obviates the need for meaningful discourse between the parties.

Reflection on the two categories outlined above, i.e., investigator-potential subject relationality and the use of
the consent form as a recruitment method, points to the necessity of the recognition and acceptance of the outsider, or stranger, role that is assumed by the potential clinical trial subject.

If the role of the stranger, or outsider, for the potential clinical trial subject is not appreciated, less than desirable results can be expected. The primary threat is that the potential subject will not be given a chance to begin and develop any meaningful relationship with the investigator before actually consenting to participate in the project, coupled with the danger of failure to recognize the potential subject's long-term consent rights. That is, the potential subject is an outsider to the system, and so is the subject as well.

The issue here is not to negate or override the individual participant's status as outsider. To do so is to ignore the reality of the clinical trial scenario. The potential subject and the actual subject are certainly both outsiders. Rather, the issue is really how this outsider status may best be realized and appreciated. That is, recognition of outsider status must be effected in a workable fashion, or else the true identity of the potential subject will not be appreciated.
Human experimentation

In Chapter two I explicating the notion of clinical trials as endeavors of human experimentation. Essentially, it is the existence of the rather rigid protocol that gives the project the designation of "experiment," and not the experimental nature of the investigational drug per se.

Others have commented on the notion of the element of human experimentation in clinical trials, and warn essentially against the use of clinical trial subjects as means to an end. One would indeed be hard pressed to deny that generally clinical trial subjects are used as means to an end. In fact, the very nature of the clinical trial seems to require this "means to an end" philosophy. The use of persons as means to an end becomes problematic, however, whenever one thinks in terms of persons being utilized as merely means to an end. An autonomous choice to be used as a research subject does not negate the basic humanity, or any rights or privileges attached to this status, of the research volunteer.

In addition to creating a predisposition for the treatment of human subjects as means to an end, the project protocol also eliminates or reduces any element of treatment for the subject qua patient. Treatment is a dynamic process that requires freedom of decision by both the investigator...
and the subject. This freedom is lacking in the clinical trial scenario, as the protocol dictates all dosage adjustments, concomitant medications, etc.

If the human experimentation element of the clinical trial informed consent process is overlooked, one can expect baleful results. The ethical issues inherent in using human beings as means to an end are well documented, and were explicated in Chapter one’s literature review. The informed consent of the potential subject, presumably giving permission to be used as a means to an end, does not obviate the need for protection from being used merely as a means to an end. This distinction is critical, but too easily overlooked by those proclaiming rather naively that humans should never be used as means.

Failure to appreciate fully the human experimentation element of the clinical trial informed consent paradigm can also lead to a false notion of the clinical trial as a method of treatment. This is especially troublesome in the area of life threatening conditions for which there is no known cure, e.g., AIDS. When compared to no treatment at all, the idea of receiving an active, although experimental, drug can well be seen to be more a matter of treatment than of research. But again, it isn’t the experimental nature of the new compound that dictates experimental status for the clinical trial, but rather the lack of negotiable boundaries
in the relationship between investigator and subject—
boundaries that are necessary for any type of therapeutic
paradigm.

Reflection on the elements of the clinical trial
informed consent paradigm gives rise to questions that may
be useful in offering analysis and prescriptive advise as to
implementation of optimal clinical trial informed consent.
These questions may be stated as: How may fairness be
assured in the paradigm?, and, How may the potential
clinical trial subject, as outsider, be treated so as to
appropriately recognize and act ethically upon his or her
unique status within the clinical trial informed consent
paradigm?

These observations and questions point to a deeper,
more meaningful scheme in clinical trial informed consent
than the transaction itself. The analysis of the deeper
structure of the paradigm demonstrates that the categories
of recruitment and outsider collapse around the issues of
institutional structures and care for the stranger. The
third category, human experimentation, gives force to the
argument that deficiencies in clinical trial informed
consent systems and methods of implementation should be
addressed. The human experimentation element of the
clinical trial demands that ethical thought drive the
decision making apparatus for clinical trial informed
consent, and reminds us, when properly understood, of the seriousness of the venture.

I will now suggest that the paradigm categories of recruitment and outsider possess an affinity with the respective justice and love thought of Rawls and Ramsey—a claim that bolsters the basic thesis that the theologically trained medical ethicist is uniquely qualified to address these issues.

As stated earlier, the medical ethicist who has been trained within a religious studies curriculum is uniquely qualified to address this issue, and hence these questions. This claim rests upon the affinity present between two major sources for ethical study within the theologically trained medical ethicist’s background and the elements of the clinical trial informed consent paradigm. There exists a Tillichian-like correlation between the major ethical issues and questions of the paradigm and the models and concepts of love and justice as espoused by Paul Ramsey and John Rawls. Rawls and the institutional structure

The thought of John Rawls, although himself a secular philosopher, is frequently invoked by theological ethicists and theologically trained medical ethicists. Further justification for the use of Rawls’ theory of justice as
fairness may be found in the historical use of Rawls by health policy scholars. While this dissertation focuses on the notion of clinical trial informed consent as opposed to health care in general, a brief analysis of Rawlsian applications in health care will provide useful background material. This background will prove helpful in further analyzing the concept of Rawlsian justice and clinical trial informed consent. Although clinical trial informed consent is not strictly speaking a health care contingency, one must be mindful of the fact that clinical trials are always conducted within the health care system. Further, a comparison of the standard applications of Rawls' thought to my own conclusions further substantiates the claim that this study is breaking new ground.

Rawls is undoubtedly one of the most widely quoted contemporary philosophers. His major work, *A Theory of Justice*, appeals to scholars and practitioners of philosophy, social sciences, religion, and economics. Rawls describes his primary aim as presenting a theory of justice that "generalizes and carries to a higher level of abstraction the familiar theory of the social contract as found, say, in Locke, Rousseau, and Kant." Rawls' resulting theory, which he refers to as "justice as fairness," is offered as an alternative to teleological theories of justice.
Rawls proposes that it is possible to determine an ahistorical method of choosing principles by which societal conflicts may be resolved. By utilizing Rawls' concept of the original position, one can imagine what rational persons would choose as principles of justice, provided that the contractors are indeed disinterested parties. To insure this disinterested nature of participation, Rawls requires the contractors to be blind to their own particular situations in society—a blindness referred to as the "veil of ignorance." Thus the social contractors are not aware as to what will be their race, gender, economic status, or other characteristics.

Rawls asserts that such rational disinterested contractors would choose the following two principles as a basic structure of justice:

1) Each person is to have an equal right to the most extensive total system of equal basic liberties compatible with a similar system of liberty for all.

2) Social and economic inequalities are to be arranged so that they are both:
a) to the greatest benefit of the least advantaged, consistent with the just savings principle, and
b) attached to offices and positions open to all under conditions of fair equality of opportunity.

Rawls avoids, or at least does not directly address, the application of his theory to health care issues. Other
scholars, however, have attempted to apply a Rawlsian perspective to health care delivery, usually within the context of health care rights.⁶⁸

The notion of a basic right to health care is asserted in the preamble to the constitution of the World Health Organization:

The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.⁶⁹

Further, the United Nations Universal Declaration of Human Rights declares:

Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including, food, clothing, housing and medical care and necessary social services.⁷⁰

One would be somewhat hard pressed to define these statements in workable terms. For instance, what does "the highest attainable standard of health" mean? Is one to assume that all persons are to receive the same health care allocation? Does "health" refer to perfect health or a reasonable compromise between disease and normal functioning? Should those less fortunate on the socio-economic scale share in the same dollar-for-dollar
allocations for health care as the wealthy, regardless of their respective health statuses?

In addressing these and other questions, ethicists, philosophers, and others interested in health policy have looked to the applicability to health care of Rawls' concept of justice as fairness. Such an application depends in large measure on how one views the priority of health care within the Rawlsian scheme of justice. An analysis of various invocations of the use of Rawls' theory in issues of resource allocation as well as the right to health care reveals three basic categories of thought: 1) Health care may be perceived to be a primary social good, and thus a right to health care could be argued along the same lines as a right to equal basic liberties; 2) Health care institutions may be considered as background institutions charged with providing fair equality of opportunity; and 3) Health care services may be viewed as goods available for purchase by one's individual shares of the social product.71

The first strategy is best represented by the argument forwarded by Ronald M. Green in "Health Care and Justice in Contract Theory Perspective." Green argues that health care should be considered a primary social good along with rights and liberties, powers and opportunities, and income and wealth.72 Because of the priority of health, Green argues, contractors in the original position would "opt for a
principle of equal access to health care; each member of society, whatever his position or background, would be guaranteed an equal right to the most extensive health services the society allows."73 Thus Green calls for the establishment of a third principle of justice to be added to the Rawlsian scheme—a principle guaranteeing the right of equal access to health care.74 This principle would of necessity be ordered lexically prior to the difference principle, as "contract parties could be expected to separate access to health care from income considerations."75

In a cogently argued rebuttal, John Moskop challenges Green's concept of a third principle of justice. Arguing that such a notion would require substantive changes in the Rawlsian scheme, Moskop asserts that the resultant violation of the integrity of justice as fairness would lead to a "slippery slope" effect in which principles specifically addressing other basic needs would have to be formulated as well.76

Green's theory, and to a lesser extent Moskop's criticism, eschews the fact that Rawls clearly addresses the status of health care as a good. In the same paragraph as his definition of primary social goods, Rawls assigns to health the status of "natural good," i.e., "although their possession is influenced by the basic structure, they are
not so strongly under its control." Thus Rawls himself, while not directly addressing health care allocation, nonetheless appears to rule out the inclusion of health as a primary social good. Green’s notion of a third principle of justice, while undoubtedly appealing to those with special health care needs, would appear to be a contradiction of the Rawlsian scheme rather than an addition to it.

The second strategy, which calls for the inclusion of health care institutions in the list of background institutions charged with guaranteeing fair equality of opportunity, is represented by the thought of Norman Daniels. Daniels’ basic assertion is that health care is best viewed as a facilitator of an individual’s opportunities. Since illness and injury restrict what Daniels refers to as "normal species functioning," it follows that acts and institutions that work to alleviate these contingencies are morally prior to acts and institutions designed more for pleasure or voluntary consumption.

The third strategy of applying Rawls to health care involves the notion of health care services as goods available for purchase. Proposed by Charles Fried In Right and Wrong, this strategy relies heavily upon the notion of the uncertainty of health care needs. Some individuals live long and complete lives unencumbered by serious accident or
illness. For these persons, a basic minimum of health care would be sufficient to address their needs. There are others, however, who need constant medical attention from birth—attention that requires far greater resource utilization than is available in any standard concept of a basic minimum.

Arguing that one may purchase insurance to cover any unexpected health care contingency, Fried claims that the risk of special needs would then be spread among the participants. The resulting health care rights claims would only be applicable for services for which one was prudent enough to purchase insurance protection."

None of the three strategies that have been utilized in the application of Rawls' justice as fairness model to health care delivery provide clear insight into the problems of clinical trial informed consent. However, the failure to derive a suitable Rawlsian rights-based scheme for informing this paradigm does not eliminate any usefulness of a Rawlsian construct in such cases. For one to appreciate the notion of justice as fairness as applicable to the paradigm, one must return to a more basic concept than the material allocation of goods and services, whether health care related or otherwise. For this we must return to my earlier argument for the importance of the institutional elements present in the recruitment category of the paradigm of
clinical trial informed consent, e.g., the hospital, investigator-subject relationship, and the role of research in society. Rawls can be helpful in my analysis, but only within the framework of what he terms the "basic structure."^80

The basic structure is the primary subject of Rawls' notion of justice, and is represented by the background institutions that perform and insure the production and regulation of benefits and burdens:

By major institutions I understand the political constitution and the principal economic and social arrangements...Taken together as one scheme, the major institutions define men's rights and duties and influence their life-prospects, what they can expect to be and how well they can hope to do.^81

Rawls admits that the concept of the basic structure is vague, and that the justification for including any given institution is unclear.^82 While not overly concerning himself in A Theory of Justice with the unclarity of the notion of the basic structure, Rawls squarely addresses the issue in a later work. "The Basic Structure as Subject" was written in a effort to further explicate Rawls' notion of the basic structure.^83

Central to Rawls' basic structure scheme is the supposition that any distribution of goods is just only if the structure of the distributional system is fair.^84 Using
voluntary market exchange as an example, Rawls emphasizes that it is only within the framework of the basic structure that society can expect to correct inequities in the distribution of goods and services.

According to Rawls, restrictive rules on individual agents are insufficient to effect the necessary corrections, as individuals are either incapable or unwilling to see the significance of their failure to make the corrections. Thus the basic structure itself is seen by Rawls as the construct that "should make the corrections necessary to preserve background justice."85

The notions of regulation and correction are critical in Rawls' conception of the basic structure. It is not enough to establish just background institutions; these same institutions must constantly be reviewed, criticized, and changed. Society is an ongoing process, and what is today a just institution may well be unjust for the next generation.86

My thought thus far has attempted to lead to the thesis that a Rawlsian interpretation of justice, provided that one does not concentrate only within an allocational or distributive perspective, possesses an affinity, or correlation, with the clinical trial informed consent paradigm category of recruitment. I will now look to a more
specific examination of Rawls that will provide a framework for viewing this critical aspect of the clinical trial informed consent paradigm within the context of the basic structure of society.

Specifically, there are two components of the basic structure, market economy and government, which apply directly to this analysis. It is evident that Rawls favors a voluntary market economy, with one notable albeit predictable qualification. A voluntary market is fair only if there has been a fair antecedent distribution of goods and services.87 This would presumably apply to the institutional structures present in my earlier hypothetical case of the university clinic patient being recruited into a clinical trial. Assuming that the requisite background institutions are just, Rawls points to two principal advantages to a market system. First, a voluntary market system is more efficient than other systems of rationing, although in reality never actually achieving strict efficiency as defined by classical economic theory. Nevertheless, a voluntary market does approach the theoretical model of efficiency.88 Second, and probably more important, a voluntary market is seen by Rawls as being consistent with his first principle (equal liberty) as well as part (b) of his second principle (fair equality of opportunity).89 Freedom of choice in careers and
occupations, as well as the decentralization of economic power, points to the conformity of a voluntary market to the Rawlsian scheme.

The appropriateness of a voluntary market model for clinical trial informed consent relates primarily to the voluntary nature of clinical trial participation, and less to the notion of the clinical research system as a technically efficient market. Society relies neither upon conscription nor any attempt to equally distribute the burdens and risks of clinical trial participation. Rather, persons are theoretically free to participate in clinical research projects according to their own motivations and decisions.

In addition to a voluntary market structure, Rawls also calls for an intricate scheme of government. Optimally, government is to be designed in such a way as to guarantee just distribution of goods and services—in other words, in accordance with the two principles of justice. Rawls proposes four distinct branches of government, each consisting of "various agencies, or activities thereof, charged with preserving certain social and economic conditions." The allocation branch serves to prevent "unreasonable market power" and to insure healthy competition. Further, this branch is charged with the task of correcting market failures that occur whenever prices do
not efficiently measure social costs and benefits. In cooperation with the stabilization branch, which attempts to insure full employment, the allocation branch is also responsible for maintaining the general efficiency of the market. 93

The transfer branch considers needs and how they relate to other claims, and regulates the distribution of needs-based claims in the form of suitable minimums. 94 Finally, the distribution branch functions as a means of insuring justice by a scheme of taxation and regulation of property rights. 95

Rawls does not propose that his theory be used to require equal access to any goods. The basis of his thought is that background institutions comprising the basic structure of society be formulated in such a way as to insure a just process of distribution of both burdens and benefits.

My analysis now shifts to the question of whether the two components of the basic structure that are particularly relevant to a study on clinical trial informed consent, i.e., voluntary market and government, satisfy the requirements of the Rawlsian notion of justice as fairness. It would appear that the American free market scheme of voluntary participation in clinical trials would be in
accord with Rawls' view that a voluntary market, via its efficiency and consistency with the notions of equal liberty and fair equality of opportunity, is indeed consistent with the implications of the two principles. This argument is strengthened by Rawls' inclusion of health as a primary good, and the fact that the benefits that are to redound to the least advantaged are likewise to be considered as primary goods. Thus both the benefits and burdens of medical research could be applicable to a Rawlsian analysis, and would be affected by basic structure considerations. One could argue that Rawls' classification of health as a natural primary good rather than as a societal primary good would preclude the consideration of health care institutions as components of the basic structure. However, beyond distinguishing between social and natural goods as a matter of classification, Rawls does not differentiate between the two regarding their applicability.

The government's involvement in the clinical trial informed consent paradigm is primarily that of the Food and Drug Administration's Institutional Review Branch. Charged with insuring the integrity of the clinical trial informed consent process in the United States, this branch of the FDA is essentially a regulatory and enforcement division. The government's involvement in clinical trial informed consent implementation, which most would agree is warranted,
nonetheless results in an increased bureaucratic process by both the agency and the investigator. This burden does not, however, negate the necessary protective function of the FDA—a function that helps insure, in the words of Daniels, "normal species functioning." 98

My explication of the various rationales for a rights-based Rawlsian analysis of health care schemes has led to an examination of the applicability of the basic structure to the notion of clinical trial informed consent. It appears evident that Rawls’ philosophy does indeed possess an affinity to the category of recruitment in the clinical trial informed consent paradigm, but only from the perspective of the basic structure of society. Again, when one looks beyond the formal transaction of clinical trial informed consent, one finds that clinical trial recruitment occurs within a matrix of institutional forces and structures. The free market voluntarism of clinical trial participation, as well as the protective function of the government, i.e., the FDA, appears to be consistent with Rawls’ notion of just background institutions.

A caveat is in order whenever one argues for the inclusion of Rawls’ theory in any analysis of a concrete situation. There is a temptation to view background institutions as rigid and static. Rawls emphasizes, however, that the basic structure is best viewed within the
context of an ongoing social process—a notion that reminds us to insist on constant review, criticism, and change.

The particular components of the basic structure that apply to the clinical trial informed consent paradigm, i.e., government and the voluntary market, must remain just in order to facilitate a fair process of research informed consent. Thus the thought of John Rawls, by providing a mechanism for the development and maintenance of just background institutions, informs the issue at hand.

Ramsey and the individual

A Rawlsian construct does not, however, address the issue of duty to the stranger—a duty, as argued earlier in this chapter, born from the role of the potential subject as outsider. Medical practitioners have defined this duty in several ways, e.g., rendering services or providing care. The notion of care, while more frequently eliciting a vision of direct attention to the clinical needs of the patient, may also be considered in the broader sense of a warrant prescribed for the medical profession—a warrant that helps determine the ethical validity of decisions and acts. Such a notion of care has been described by Paul Ramsey, and is particularly useful in medical ethics issues.
Ramsey is not the only theological ethicist whose thought has been analyzed within the context of issues of medical ethics, nor is there a scarcity of other theological ethicists who have directly addressed medical ethics issues. As stated earlier, Ramsey was chosen for this analysis primarily because of the correlation of his distinctively deontological stance of prescribing proper treatment of one's neighbor to the understanding of the clinical trial subject as outsider or stranger. A distinction must be made between Ramsey's thought on love and that directly addressing issues of medical ethics. The latter, although useful in my analysis, will be somewhat limited due to Ramsey's interest in clinical and microallocational issues rather than in the broader issues inherent in addressing clinical trial informed consent.

Ramsey's first major work, Basic Christian Ethics, codifies an ethics based upon Christian agape. For Ramsey, agape is derived from the concept of covenant faithfulness. Men are called to love their neighbor in the spirit of faithfulness, and not out of any sense of consideration of consequences. One of Ramsey's priorities in Basic Christian Ethics is to define the term "neighbor." Reminding us that the parable of the Good Samaritan instructs us on neighbor-love but not directly on the neighbor, Ramsey calls for the active loving of one's
neighbor irrespective of whether the neighbor deserves such love.\textsuperscript{102}

Taking the issue of neighbor-love to a broader scale, i.e., that of superior values, Ramsey reminds us that there are two basic questions in ethics: 1) What is the Good? and, 2) Whose Good shall prevail when a choice must be made?\textsuperscript{103} Asserting that the second question is the primary concern for ethics, Ramsey calls for the practice of agape toward the neighbor—a practice that negates the importance of erotic love or a love seeking its own reward.\textsuperscript{104}

In Basic Christian Ethics, Ramsey expounds a model of vocations based on agape. Ramsey reminds us that the Reformation served to equalize all vocations in the sight of God. No longer was there a special religious merit attached to the clergy. Using Tolstoy’s example of love, which Ramsey compares to the Sermon on the Mount, Ramsey asserts that the vocational duties of love often call for preferential treatment of certain persons over others. Ramsey sees no inconsistency in this concept provided that the preferential love is for the good of the neighbor. However, preferential treatment is not love if it results from selfish motives.\textsuperscript{105}

Ramsey further asserts that love is always in search of a social ethic in which to express itself. Finding the best
avenue for love is an example of disinterested love for neighbor. Ramsey questions whether a social order can be shaped from the norm of Christian love. Reminding us that love indeed calls for such a social policy, Ramsey asserts that the acid test for social change is to first determine the neighbor's need. It is within this spirit that one can sway the current customs and institutions toward disinterested love for neighbor.¹⁰⁶

Basic Christian Ethics rather forcefully argues against the use of rules, a stance that is modified by Ramsey with the publication of Deeds and Rules in Christian Ethics. This later work raises the issue of working through rules, with Ramsey arguing that there can be no Christian social ethics without agape-based rules of practice.¹⁰⁷ Our task is to seek not only our neighbor's needs but also to determine what love requires as a social practice.¹⁰⁸

One of Ramsey's central questions in Deeds and Rules in Christian Ethics is how to categorize the ideal of agape as an ethical system. Whereas other ethical systems depend upon either a deontological or teleological motif, Ramsey argues that agapism deserves a third normative category of ethics. Ramsey suggests that agapism, while distinct from deontological and teleological systems, is much closer to the former than to the latter. Christian love defines what
is to be effected among men, and does not define the good in a sense of utility or desert.\textsuperscript{109}

There is no easy blending of Ramsey's theological ethics into his medical ethics. This has as much to do with style as with substance. For instance, \textit{The Patient as Person}, Ramsey's first major treatise on medical ethics, is not so much a systematic treatment of conceptual ideas as it is a disconnected series of diverse topics.\textsuperscript{110} Ramsey's interest in medical ethics is clearly centered within the framework of clinical medicine. Less important for Ramsey are macroallocational issues of resource distribution.\textsuperscript{111}

In "The Ethics of a Cottage Industry in an Age of Community and Research Medicine," Ramsey addresses what he refers to as medicine's social requirement to do the greatest good for the greatest number of present and future patients together. Ramsey asserts that one must often determine rightness and/or wrongness of medical actions or policy irrespective of this utilitarian approach. Reminding us that there is no "unseen hand" that assures the ethical justification of policies and procedures designed to produce much aggregate good, Ramsey asserts that moral judgment must be used in determining the adequacy of any proposal. Ramsey further calls for an attitude of partnership between recipient and provider—a recognition that we are all bound by a covenant of faithfulness that allows us to be "joint
adventurers" toward medically useful goals. This notion of partnership will form a cornerstone in my analysis, as I will later argue for the existence of a covenant relationship between the investigator and the clinical trial subject.

One must proceed with caution when attempting to apply theological insight to concrete problems, whether they be societal, medical, or otherwise. Ramsey himself warns against the use of religion to prescribe specific social policy. A central aim of this dissertation, however, is to demonstrate the correlation between Ramsey's notion of neighbor-love and the paradigm category of outsider or stranger. Henceforth, this section of the analysis will proceed not with the presupposition that Ramsey's thought may offer a direct answer to a rather specific medical ethics issue, but rather with the acceptance of Shriver's notion that:

The Hippocratic oath suggests that service to any person in need is ...a professional presupposition that links medicine at once with those traditions in religion that sanction unselfish love as the highest motive of human relationships.

The remainder of this chapter will return to the sources outlined earlier, but with a specific focus on Ramsey's notions of love and service—notations derived from his distinctively Christian ethical vision.
Again, in *Basic Christian Ethics* Ramsey forwards the notion that concern for one’s fellow man is best represented by the notion of agape, or unselfish love for one’s neighbor. Ramsey begins this thesis with a critical look at the distinction between the righteousness and love of God and the reign of the Kingdom of God. In contrast to Emil Brunner, Ramsey relies on the biblical conception of righteousness rather than on moral norms derived from reason.

Ramsey describes Jesus’ admonition regarding anxiety to be grounded in his conviction concerning the Kingdom of God. Eschatological predictions of Jesus, as exemplified by the Beatitudes, are interpreted by Ramsey to indicate Jesus’ contention that the Kingdom of God was coming regardless of man’s readiness or lack thereof. This eschatological reference is stressed by Ramsey to have an enormous qualifying impact on Jesus’ ethical teachings; grave doubt is expressed concerning the validity of lifting the ethical teachings of Jesus from their original context. One may assume that it is this doubt that causes Ramsey’s hesitation to directly apply Jesus’ ethical teachings to concrete social problems.

One could well argue that Jesus’ instructions for love of neighbor are invalidated because of their apocalyptic
origin. However, Ramsey reminds us that "genesis has nothing to do with validity," and that the worth of agapaic love for neighbor is far superior to any "miscalculation of time" on the part of Jesus. Rather, the ethical teachings of Jesus are relevant precisely because of their effective focus on the immediate neighbor-needs of individuals apart from the competing claims of others.

In yet another example of addressing the needs of the individual, Ramsey states that we are not to confuse love of neighbor for love of mankind in general. The former encourages love of neighbor for his or her own sake, and not for the sake of a more global disposition. Love for neighbor for his or her own sake "insists upon a single-minded orientation of a man’s primary intention toward this individual neighbor with all his concrete needs." Love for neighbor for his or her own sake evolves into a universal love, since any person may be the neighbor. However, any universality is implicit rather than explicit, as would be the case for love of mankind in general.

Ramsey’s notion of agape must be recast into more practical terms if one is to discover usefulness in its application to historical medical contingencies. This translation is accomplished by Ramsey’s use of agape as analogous to the concept of care for the individual qua
patient. Agreeing with the Barthian notion that "covenant-fidelity is the inner meaning and purpose of our creation as human beings," Ramsey, in *The Patient as Person*, proposes that the field of medicine is one expression of the covenant relationship that persons are called to practice with one another. Again, *The Patient as Person* may be described as a rather segmented compilation of Ramsey’s thoughts on several different issues. However, the recurrent theme of the entire volume is that of recognition of the integrity of the individual.

Ramsey’s medical ethics makes clear his supposition that agape calls for obligation to one’s neighbor, and not any sense of social usefulness, to be the starting point for ethical reflection. Further, it is clear that Ramsey holds covenant-faithfulness, in the form of duty to care for one’s neighbor, to be morally prior to any consideration of consequences:

In the language of philosophy, a deontological dimension or test holds chief place in medical ethics, beside teleological considerations. That is to say, there must be a determination of the rightness and wrongness of the action and not only of the good to be obtained in medical care or from medical investigation.

Ramsey’s self-description as an "ethicist of principles," and therefore not a consequentialist, must not be viewed as an attitude confined to his later work
within the field of medical ethics. In *Basic Christian Ethics*, for example, Ramsey asserts that any good that results from an act, other than the primary good for the neighbor's sake, is to be regarded as a "quite unintended by-product."\(^{126}\) A further, much stronger argument against the consideration of consequences is found in *Deeds and Rules in Christian Ethics*, in which Ramsey proclaims that "the reduction of Christian ethics to teleology is nearly the same thing as abandoning it."\(^{127}\)

Ramsey, responding to criticism that his notion of covenant-care is a movement away from the more basic notion of agape, and is related to his interest in medical ethics, refers his critics to the final chapter in *Basic Christian Ethics* in an effort to establish the priority of covenant even in this early work.\(^{128}\) However, a careful reading of Ramsey's notion of community reveals this concept much earlier than in his closing chapter.

Ramsey directly addresses the issue of community in *Basic Christian Ethics*. While economists would argue that communities are essential for the exchange of services, Ramsey asserts that community is essential in the realm of spirituality as well. The primary difference between the two is that an economic community allows men ultimately to seek only their own good, whereas spiritual community requires that the good of the neighbor be sought.
Besides Christian love, Ramsey describes two concepts that may be applied to the creation of community among persons. One may opt for either a self-centered or value-centered paradigm. Ramsey's self-centered paradigm is best represented by Jeremy Bentham, who assumed that by living under the law and its attendant threats of retributive justice one would be forced into living within the best interest of society at large. By calculating the price to be paid for violating legal and societal sanctions, the individual is more apt to contribute to the good of society. That the individual's contribution is entirely self-centered does not preclude the possibility that positive acts will be performed. On the contrary, the individual will contribute positively out of the expectation of his own good being enhanced.

On the other hand, one may look to a more value-centered approach to the derivation of communities. Using J.S. Mill's utilitarianism as an example of a value-centered approach, Ramsey argues that such an assertion is as naive as it is confusing. For such an argument as Mill's ignores Ramsey's basic question of Christian ethics, i.e., whose good it shall be when a choice must be made.

Ramsey does not allow self-centered or value-centered derivation of duties to be primary in the creation of
community among men. Rather, he reaffirms his notion of concern for the neighbor for his own sake as the primary impetus for creating such community. Spiritual community never springs from love of value or love of self.

Ramsey structures his thought on community by asserting that there are two categories of community—those that already exist and those that need creating. Education plays a major role in preserving an already existing community of individuals. This education is basically in the form of showing the individual his or her own interest in the preservation of a community of mutual interest.

On the other hand, the creation of community where none exists poses quite a different problem. Unlike the case of the already existing community, enlightened self-interest is of no value in the creation of community. Likewise, principles of distributive justice are of little value when no community of mutual interest exists.129

It is at this juncture that Ramsey solidifies his thesis that it is the work of Christian love that creates community among persons. Christian love enters the realm "where dwell the desperate and the despised outcasts from every human community, and brings community with them into existence."130
With his insistence that the creation of community is the special role of Christian love, Ramsey does not negate the importance of such love in the preservation of community. Referring to love as the primary ingredient for the preservation of community, Ramsey allows that the ingredients of self-centeredness and mutual interest are also operative.

For Ramsey, the creation and preservation of community among persons is analogous to the recognition of another human being's worth. Thus Ramsey credits love with furthering the technological revolution in the middle ages by advancing the notion of human dignity. Machinery relieved slaves of many of their most difficult duties. Here we see the most concrete example of Ramsey's notion of the interrelatedness of economic and spiritual communities.\textsuperscript{131}

Ramsey asserts that agape is concerned only with the second question of Christian ethics, i.e., whose good it shall be when a choice must be made.\textsuperscript{132} His notion of agapaic care for the patient as individual, which has its origins in his earlier writings but finds its fullest expression in his treatment of medical ethics issues, possesses an affinity to a paradigm that recognizes the potential clinical trial subject as outsider or stranger. Further, Ramsey's notion of community as the result of love
practiced among persons, when framed with his argument that love and care are analogous, serves as a useful model for cooperative relationships between investigators and potential subjects.

It would therefore appear reasonable to appeal to Ramsey's thought for guidance on issues such as deficiencies in clinical trial informed consent, particularly those matters concerned with the status of the potential subject. Ramsey himself, however, generally eschews such concrete issues. On two different occasions, in fact, Ramsey refers to questions of medical and social priorities as "incorrigible to moral reasoning"¹³³ as well as to "rational determination,"¹³⁴ concentrating instead on the distributional issues of scarce life-saving techniques. One may presume that Ramsey's reluctance to enter policy disputes results from his thesis that the primary concern of ethics is not what the good actually is, but rather whose good it shall be when a choice must be made. In order to affect policy decisions, Ramsey would presumably need to concern himself more with the question, "What is the good?" rather than concentrate only on the question "Whose good shall it be when a choice must be made?" Responses to both of these questions have an impact upon the relationality between investigator and the potential clinical trial subject.
Ramsey, although not directly addressing potential clinical trial subjects as outsiders or strangers, cogently argues that patients need to be viewed and treated as individuals, and prescribes a method for agapaic care of persons in need of medical treatment. Since clinical trials are always conducted in a medical environment, it is not too broad a leap to suggest that the potential clinical trial subject be viewed and treated in the same fashion. In this respect, Ramsey's thought does indeed possess an affinity, or correlation, to the clinical trial paradigm category of outsider.

While I agree that Ramsey's thought does not allow one to formulate concrete social or medical policy in the area of clinical trial informed consent, this does not negate any contribution that covenant-care may make to such contingencies. Any criticism at this stage is not aimed at Ramsey's ethical construct, but rather at his failure to recognize its applicability to broader issues.

Conclusion

My analysis of the three paradigm categories of clinical trial informed consent points to basic, core issues of institutional forces, concern for the stranger or outsider, and an appreciation for the human element of clinical trials. These notions are present at a deeper
level in the clinical trial informed consent process than the historically identifiable transaction that occurs between the investigator and the potential subject. These basic issues, which reflect the reality of clinical trial informed consent as the recruitment of outsiders into the realm of human experimentation, point to a system that is both institutional and personal. Clinical trial informed consent does not occur within a vacuum, nor is it simply a transaction between parties. Rather, clinical trial informed consent is a personal process that occurs within a complex matrix of institutional forces.

The thought of John Rawls has been demonstrated to possess an affinity to the basic issue of institutional forces at work in the clinical trial informed consent scenario. Rather than argue from a rights-based claim, as is usually the case when one calls on Rawls' support in a health policy analysis, I have instead focused on Rawls' notion of the basic structure of society—a basic structure that requires constant monitoring and modification if the institutional forces are to remain fair. Further, Paul Ramsey's notion of agape as care has been correlated with the needs of the potential clinical trial subject qua stranger. Care completes the formula that springs from the paradigm's analysis, i.e., that both institutional forces
and the notion of outsider must be addressed if deficiencies in clinical trial informed consent are to be corrected.

In discussions on clinical trial informed consent, the contribution of the theologically trained medical ethicist is thus two-fold. On the one hand, he or she may address the institutional matrix of clinical trial informed consent by utilizing Rawls' basic structure arguments. Similarly, the theologically trained medical ethicist may also provide insight and guidance into the personal element of the clinical trial informed consent process by use of Ramsey's notion of care for the individual. This positing of Rawls and Ramsey within the paradigm categories, which is analogous to Tillich's perceived dichotomy in the relationship between the secular and the sacred, provides the theologically trained medical ethicist with a dual method of helping diagnose and remedy the clinical trial informed consent process.

Ramsey's distinctively Christian vision obviates the need to defend his inclusion in the theologically trained medical ethicist's armament for addressing specific issues. On the other hand, the inclusion of the secular philosopher Rawls may be questioned. However, as was stated in Chapter one, Rawls' usefulness to the theologically trained medical ethicist is not dependent on any purely theological significance of his work. Rather, Rawls' notion of the
basic structure of society provides a corrective model for
the complex institutional structures of the clinical trial
informed consent paradigm. This model, when coupled with
Ramsey's notion of care for the individual, allows the
theologically trained medical ethicist to enter and
facilitate discussions on clinical trial informed consent
issues. Further, the inclusion of Rawls in a theological
critique responds to Reinhold Niebuhr's assertion that an
ethical system

must give guidance not only in terms of the ultimate
possibilities of life, for which sacrificial and
forgiving love is the norm, but must also come to terms
with the problem of establishing tolerable harmonies of
life on all levels of community.135,136

Rawls' "non-theological" status does not make him
morally irrelevant. This is especially true for the
theologically trained medical ethicist, who is faced with
the challenge of mediating issues of faith and culture.
Endnotes to Chapter three


4"Using Instructive Videotapes to Increase Patient Comprehension of Informed Consent."

5*Ethics and Regulation of Clinical Research*, p. 142.


12"Patient Recruitment and Enrollment into Clinical Trials," p. 35.

13"Factors That Motivate Healthy Adults To Participate in Phase I Drug Trials," p. 109.
18"Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, Fundamentals of Clinical Trials (Boston: John Wright, 1983), p. 100.


16Kirkpatrik's study involves only the Phase I scenario.

17"Factors That Motivate Healthy Adults To Participate In Phase I Drug Trials," p. 113.


19Ethics and Regulation of Clinical Research, pp. 69-93.


23"Informed Consent and Moral Integrity."

24"Human Experimentation in Historical and Ethical Perspectives," pp. 1439-1440.


29Ethics and Regulation of Clinical Research, p. 77.


32 "Caring for the Silent Stranger: Ethical Hospital Care for Non-English Speaking Patients."


34 "Caring for the Silent Stranger: Ethical Hospital Care for Non-English Speaking Patients."


36 *Ethics and Regulation of Clinical Research*, pp. 134-140.


39 "Informed Consent and Moral Integrity."


42 "Informed Consent and Moral Integrity," p. 117-123.

43 "Informed Consent in Research and Practice," p. 1229.
"Consent, Informed Consent and the Consent Form."


Ethics and Regulation of Clinical Research, pp. 134-140.


Ethics and Regulation of Clinical Research.


The Myth of Informed Consent: In Daily Practice and In Clinical Trials."


Human Experimentation in Historical and Ethical Perspectives."


Ibid., pp. 136-142.

Ibid., p. 302.


Constitution of the World Health Organization (Official Record--WHO 2, 100).


Ibid., p. 117.
"Ibid., pp. 121-123.

Ibid., p. 118.


A Theory of Justice, p. 62.


A Theory of Justice, pp. 7-11.

Ibid., p. 7.

Ibid., p. 9.


Ibid., p. 160.

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Ibid., p. 161.

A Theory of Justice, pp. 270-274.

Ibid., p. 272.

Ibid.

Ibid., pp. 274-284.

Ibid., p. 275.

Ibid., p. 276.

Ibid.

Ibid.

Ibid., pp. 277-280.

Ibid., p. 62.
97 Ibid.
99 The Basic Structure as Subject, p. 164.

101 Ibid., pp. 133-152.
102 Ibid., pp. 92-103.
103 Ibid., p. 114.
104 Ibid., pp. 114-115.
105 Ibid., pp. 153-190.
106 Ibid., pp. 326-366.

108 Ibid., pp. 133-144.

110 The Patient as Person: Explorations in Medical Ethics.


114 Ibid.
115 Basic Christian Ethics, p. 35.
116 Ibid., p. 41.
117 Ibid., p. 44.
Ibid., p. 94.

Ibid., p. 95.

Ibid.

The Patient as Person: Explorations in Medical Ethics, p. xii.


The Patient as Person: Explorations in Medical Ethics, p. 2.


Basic Christian Ethics, p. 116.


Basic Christian Ethics, pp. 246-248.

Ibid., p. 242.

Ibid., pp. 246-248.

Ibid., pp. 114-115.

Ibid., The Patient as Person, p. 240.

Ibid., p. 268.

CHAPTER FOUR

PRESCRIPTIVE RECOMMENDATIONS

Introduction

My analysis of the clinical trial informed consent paradigm, and the correlative relationship present between the categories of the paradigm and the thought of Paul Ramsey and John Rawls, suggests that the theologically trained medical ethicist is indeed uniquely qualified to address the situation of clinical trial informed consent. I will now proceed to the dissertation's prescriptive element, i.e., specific solutions that reflect the relationality between the paradigm categories of clinical trial informed consent and the thought of Rawls and Ramsey.

Rawls calls for the constant review, criticism, and correction of the background institutions of society, for "adjustments in the basic structure are always necessary." In Chapter three I stressed the importance of viewing the voluntariness and regulation of clinical trial informed consent as background institutions within the paradigm, and as such components of the basic structure.
The Institutional Review Branch of the Food and Drug Administration, functioning as the primary government agency dealing with matters of clinical trial informed consent, possesses not only practical expertise in the implementation of policy, but also, via enforcement powers, the ability to assume that appropriate policy is implemented. The mission of this government agency can only be optimally realized via the Rawlsian notion of adjustments in the basic structure. Otherwise, any prescriptive advice and enforcement action will be directed only to the potentially ritualistic practice of appreciating clinical trial informed consent as a documentation process.

Ramsey, on the other hand, has focused on the individual. Through his agape-based ethics of care, Ramsey has asserted that one has an obligation to address the needs of one's neighbor—a designation that would presumably include the potential clinical trial subject qua outsider.

How may Ramsey's agape-based deontology be applied to such a seemingly secular contingency as clinical trial informed consent? First, it is necessary to recall Ramsey's notion of covenant-care—a concept derived from his notion of agape. For Ramsey, covenant-care is the "inner meaning and purpose of our creation as human beings" and demands a moral relationship between the individual, his or her
neighbor, and institutions with which he or she is associated.²

In medical ethics issues, covenant-fidelity relationships are not limited to the physician-patient encounter, but may involve the investigator-subject relationship as well. This covenant between investigator and subject recognizes the notion of clinical trial informed consent as the recruitment of outsiders into the realm of human experimentation.

The successful application of any theory of a covenant-fidelity relationship between the investigator and the potential and actual subjects rests with one’s interpretation of the purpose of the covenant. If the function of the covenant relationship is that of producing a given good, one is faced with the challenge of applying deontology to a concrete medical issue—a task deemed inappropriate by Ramsey.³ Rather, one must look to Ramsey’s notion that:

...love has to do with the very nature of love itself, it does not simply provide love with another object—the neighbor—in whom one’s bonum should still be sought. Christian love in its nature gives some good, it is not primarily concerned to seek good. It is deontologically, as a matter of obedience, related to the neighbor as such; it is not teleologically, as a matter of desire, related to some bonum.⁴
This notion of love, when viewed within the context of Ramsey’s assertion that the primary concern of Christian ethics is the determination of whose good it shall be when a choice must be made, suggests that Ramsey’s fundamental concern is the relationship between parties.

Viewed within the notion of relationship between parties, and especially the relationship between the investigator and the potential subject, my earlier argument for the usefulness of Ramsey’s thought in informing a discussion on clinical trial informed consent appears valid. It would further appear that Ramsey’s emphasis on covenant-fidelity could be translated into a notion of an obligation of virtue on the part of the investigator. That is, the investigator is called to develop and maintain a decision making apparatus that recognizes the potential subject as neighbor.

The inclusion of Rawls and Ramsey in offering insight into the clinical trial informed consent situation is thus defensible. I will now move on to specific, prescriptive suggestions for change. These suggestions are grounded within the relationality between the paradigm categories of clinical trial informed consent and the love and justice explications of Ramsey and Rawls. However, it must again be stressed that this study is not an application of the thought of Ramsey and Rawls to the issue at hand. These
prescriptive suggestions are not, for instance, based upon how Ramsey or Rawls might view a particular situation. Rather, these suggestions are derived from reflection on the broad notions of care and justice in the clinical trial informed consent scenario.

Covenant relationships in clinical research

One suggestion for improving the validity of the clinical trial informed consent process is to effect a covenant relationship between the investigator and the potential subject. The notion of covenant between physician and patient has been explored. However, the investigator-potential subject relationship differs significantly. As previously mentioned, these differences between the physician-patient and the investigator-subject relationships center on issues such as the therapeutic relationship between physician and patient, the transient and temporary relationship between investigator and subject, and the negotiation of treatment boundaries that are present between the physician and patient, but absent in the investigator-subject relationship.

The significance of the difference between the two relationships lies in the boundary difference in the two scenarios. In treatment, boundaries are at least negotiable, although often not actually negotiated. In a
clinical trial, the existence of a protocol seriously limits the negotiation between the investigator and the potential subject. A covenant arrangement would serve to lessen the impact of the negation of boundary negotiability, as it would emphasize that each participant plays a major role in the research project. In fact, a covenant arrangement in effect states that neither party is more important to the project than the other—a scenario not often currently played out in clinical trial informed consent transactions.

A covenant relationship between the investigator and the potential subject is consistent with Ramsey’s notion of co-adventuring, which was described in Chapter three. Further, a covenant relationship also meets the agapic requirement of meeting the neighbor’s need—presuming that the covenant itself is based upon mutual respect.

The advantage of a covenant relationship between the investigator and the potential subject, on a practical level, is that such a relationship implies and confirms commitment between the parties—something very critical when one is dealing with issues of human experimentation. Commitment between the parties, in which both are perceived by the other as being equal, to a large extent negates the importance of the absence of negotiability of the boundaries of the relationship—a situation referred to above. This serves to insure compliance with the protocol—compliance
that is clinical research's answer to treatment boundaries. Just as the success of a treatment regimen depends heavily upon the dialectic between what the physician thinks needs to be done (treatment) and how the patient participates in that decision, by adhering to the treatment regimen; so too does the success of a research protocol, and the informed consent process preceding it, depend largely on the dialectical tension between the investigator and the subject. A subject must be an active participant in the project--clinical research is not a passive activity. However, this role is best played out in a scenario in which the subject is clearly in a covenant pact with the investigator--a relationship that, given the experimental nature of clinical drug trials, is appropriately described as "co-adventuring."

Of course, caution must be exercised to insure that in appreciating the equality provided by the covenant, the subject does not assume an allowance for noncompliance with the protocol. The non-negotiability of boundaries within the clinical trial is not something that can or should be changed, as the scientific method requires strict compliance to repeatable procedures and data collection activities. What can and should be changed is the relationality between the parties. To be consistent with Ramsey's notion of
covenant, this new relatiornality must not be merely dispositional, but must result in a mutual meeting of needs.

Individualization of communications

Another suggestion for improving the validity of the clinical trial informed consent process is to "individualize" the communication between investigator and potential subject. Levine has described this communication style for the physician-patient interaction:

The physician does not speak in a language appropriate to the average layperson, but rather to the unique individual who is the patient. Even more important, the physician listens and responds to that unique person. The physician evaluates the patient's utterances—not necessarily in the paternalistic sense of deciding whether what they are saying is rational or appropriate—but more in the sense of whether it is authentic for that person, e.g., 'I have heard George's choice but that is not like the George I know; perhaps we should pursue this matter further.'

There is no reason why investigators cannot pursue this same style of communication with potential subjects, even if these persons are strangers to the investigator. The intent behind the use of "layman's language" in informed consent is simply to insure that a person of average intelligence and education can understand the research project and its attendant risks and benefits. However, many potential subjects are far from average. Those with less education, for instance, might require more basic explanations, while
the more highly educated potential subject may wish to inquire and converse with the investigator on a more scientific or technical level. Unfortunately, "layman's language" is interpreted to mean "standard language"--a reality that blocks any effective individualization of the dialogue between investigator and potential subject.

To those who would claim that to individualize the communication between investigator and potential subject violates the notion of the use of "layman's language" in informed consent, one could argue that this requirement applies only to the consent form itself.¹⁰ The time invested in getting to know something about the potential subject for purposes of "customizing" the clinical trial informed consent process may well contribute not only to a better informed potential subject, but also to a more compliant and hence more reliable subject after the trial actually begins. Thus the benefits of such individualization extend both to a more valid informed consent process as well as to the collection of more accurate research data.

Investigator negotiation

Another suggestion for improving the validity of the clinical trial informed consent process is to insure that only the investigator actually negotiates the informed
consent of the potential clinical trial subject. Presently, the consent process is frequently overseen and completed by the study coordinator rather than by the investigator. The investigator then countersigns the consent form itself. To assume that this signature is anything other than a formality is incredibly naive.

If this suggestion were to be effected, the investigator would be required, presumably by FDA regulations, to not only be responsible for the informed consent process, but to also be the co-participant in the process along with the potential subject. That is, the investigator would enter into immediate dialogue with the potential subject, and would himself or herself explain the protocol and its attendant benefits and risks. The investigator would be a legitimate, active participant in the process preceding the potential subject's decision of whether or not to participate in the clinical trial.

This suggestion is obviously closely aligned with the notion of a covenant between the investigator and the potential subject. The early negotiation phase of the informed consent process is an ideal time for the investigator and the potential subject to not only discuss the scientific and technical nuances of the protocol, but also to get to know one another. The covenant is effected between researcher and participant much more efficiently
when both parties meet not only before any decision is made, but also before any information is disseminated.

In this fashion, the covenant is not so much between the investigator and the subject in their respective roles—roles that, because of the matrix of ideas brought to the table by both parties, are biased toward a less than desirable informed consent process and transaction. Rather, what is optimally effected is a true covenant between human beings. In this case, the investigator can communicate to the potential subject as a fellow adventurer, not as a physician qua investigator, which is the more likely scenario whenever, as is frequently the case, the investigator and subject have their first encounter at Visit One of the protocol. In many cases this occurs days or weeks after the informed consent transaction has been finalized by the study coordinator.

There is an even further practical advantage to the notion of the informed consent process being negotiated directly between the investigator and the potential subject. This is that the study coordinator, while oftentimes a nurse or other health professional, is not always in a position to provide the detailed answers to specific scientific questions that could better be addressed by the investigator. The coordinator is usually an expert in the protocol itself, e.g., how many days there are between
specific study visits, concomitant medications that are allowed, or restricted activities during the course of the study. The investigator, on the other hand, is more particularly qualified to address specific questions concerning the experimental agent itself, such as mechanism of action, similarity to other compounds, end-organ effects, etc.

One could potentially argue, with a certain degree of plausibility, that the informed consent process and transaction are legitimately delegated activities from the investigator to the coordinator. After all, investigators are as pressed for time as are other physicians. In fact, most clinical investigators perform drug studies in addition to their full schedules of private practice or academic medicine. However, one must realize that being a clinical investigator is a voluntary activity, and that the necessary time requirements should be addressed before a commitment to participate is made.

The notion of potential subject

Another suggestion is to emphasize the role of the potential subject as potential subject. This notion requires a two-part concept of the notion of potential subject. Throughout this dissertation I have referred almost exclusively to the "potential" subject. The only
exceptions have been those instances and references in which I am clearly referring to a person who has actually been enrolled in a clinical trial. Such a person is, of course, a *subject*. However, to refer to a person who is in the clinical trial informed consent process as a *subject* is not only technically premature, but also violates the integrity of the potential subject’s true status. Unfortunately, most authors have not appreciated this distinction.\textsuperscript{11}

The first nuance of the "potential subject" scenario is an appreciation for the meaning of "potential." Again, the individual is not a subject until of course actually enrolled in the clinical trial—an event generally considered to be the signing of the consent form. Second, one must fully appreciate the notion of the *subject* status of the clinical trial subject. All too often, the clinical trial subject is referred to as a "patient."\textsuperscript{12} As discussed in Chapter two, some authors distinguish between subjects and patients by bestowing subject status on normal, or healthy, volunteers in Phase I safety studies, and referring to persons enrolled in Phase II-IV trials as patients. The rationale for such a distinction is of course that persons enrolled in Phase II-IV clinical trials have the disease being studied, and are therefore "patients." Such a distinction, while correctly recognizing the subject status of normal volunteers, is nonetheless fundamentally wrong.
To refer to a clinical trial subject as "patient" is to ignore the experimental nature of the research process. That the subject indeed has the disease being studied, and hence is a "patient" in the global sense, does not mean that the individual is a patient in the clinical trial. Further, because of the propensity toward miscommunication with health professionals, the role of patient is problematic in its own right.\(^\text{13}\)

To those who would argue that insisting upon referring to participants as subjects rather than as patients is a case of semantic hair-splitting, one must again appreciate that the significance of research versus treatment lies not only in the fact that the agent being researched is experimental and hence of unknown usefulness, but also that the confines of the protocol negate any notion of treatment. The investigator is virtually stripped of his or her major decision making authority in a clinical trial. The dosages employed are fixed by the protocol, with adjustments allowed only in step-wise fashion at predetermined intervals. Investigators do not rely upon their own judgment in enrolling subjects, as they do in initiating treatment. Rather, the entry into the trial by a given subject is determined by his or her meeting the sometimes rigid inclusion and exclusion criteria—a situation also addressed
in Chapter two. Any semblance of the "patient" role quickly breaks down in such an arrangement.

By emphasizing the participant's role as one of potential subject, the person is less likely to be treated merely as a means to an end. To refer a priori to a potential subject as "subject" is to assume to know what the person's decision will be, and to a considerable extent seemingly obviates the need for informed consent itself. The presumptuous notion of this attitude cannot be overlooked. Further, the second half of this issue, i.e., acceptance of "subject" rather than "patient" status, also insures that the individual is less likely to be treated merely as a means to an end. If the potential subject is viewed as a patient, one can only assume that the traditional nature of the physician-patient encounter will be acted out, which can easily lead to a violation of the true and valid purpose of clinical trial informed consent.

Role of the institutional review board

Another suggestion for improving the validity of the clinical trial informed consent process is to require the Institutional Review Board (IRB) to approve and oversee the entire informed consent process. This, like the suggestion to fully appreciate the reality of the "potential subject," is a two-part issue. First is the issue of the IRB's
approval of the clinical trial informed consent process. At first glance, this appears to be suggesting something that the IRB is already required to do. After all, the IRB is certainly charged with responsibility for approving the consent form. The consent form, however, is only one part of the overall transaction. In fact, a major assumption in this dissertation is that the signed consent form is all too often viewed as obtaining informed consent. What I am suggesting here is IRB approval of the clinical trial informed consent process. While some IRBs may indeed address this issue, it is naive to assume that most do any more in this regard than merely check the consent form for the eight obligatory elements.

An IRB could approve a proposed clinical trial informed consent process by requiring that the investigator submit, along with the proposed research protocol and corresponding consent form, an outline of his or her plans for actually obtaining the true informed consent of the potential subject. Is the initial conversation regarding the study held between the potential subject and the investigator, as was suggested earlier in this chapter? How is the potential subject approached? Is the potential subject informed immediately that he or she is being recruited for participation in an experimental research project, or does this become known only after he or she is told that the
physician wishes to "try a new medicine on you"? Questions such as these would serve to give the IRB the information it requires for determining the validity of the clinical trial informed consent process as ethical construct, and would further minimize the potential subject being utilized merely as a means to an end.

The second part of this recommendation is that the IRB actually oversee the clinical trial informed consent transaction. There are several ways in which this could be accomplished. At the extreme, IRB members could actually witness each informed consent transaction. Since each informed consent transaction is actually a multi-faceted process, however, this would probably be impractical. IRB members simply cannot listen to every telephone call, or read every piece of correspondence between the investigator and the potential subject. Therefore, a more realistic oversight function would be that of observing a representative number of informed consent negotiations, requiring the investigator to periodically make available his or her records concerning potential subjects' responses to being asked to participate. Similarly, IRB members could selectively interview actual subjects in an effort to determine the validity of the clinical trial informed consent process. The key point here, regardless of how it is effected, is for the IRB to become involved in the
process of clinical trial informed consent, rather than, as is so often the case, to essentially just approve the consent form itself.

The advantages of such a two-fold approach by the IRB, i.e., approval of the process and overseeing of the transaction, are numerous. By approving the actual methods to be utilized in obtaining informed consent, the IRB serves to facilitate the obtaining of a more valid informed consent. If the entire process, and not just the signing of the consent form, is not subject to approval, the IRB has essentially perpetuated the myth of informed consent being the obtaining of the potential subject’s signature on the consent form. Further, such prospective approval on the part of the IRB also serves to strengthen the place of informed consent in the mind of the investigator, i.e., by reminding him or her of the seriousness of the central issue.

Similar advantages are to be found in the case of the oversight function of the IRB. Under such a scheme, investigators could not, as is frequently the case, look upon the IRB as a bureaucracy to deal with before beginning their research project, but rather as a body that is intricately involved in the clinical trial from beginning to end. Currently, even those investigators who fully appreciate the role of the IRB insofar as informed consent
is concerned, nonetheless view the IRB's involvement as essentially being limited to "approval" rather than to a continual review. Further, and possibly most important, these suggestions may serve to insure that the practice of assuming that the informed consent process begins with the potential subject reading the form and ends with his or her signature be abandoned in favor of an ongoing informed consent process that begins when the potential subject first hears or reads about the clinical trial and ends when the subject actually completes the trial.

Sponsor involvement in informed consent

Another suggestion for improving the validity of the clinical trial informed consent process is to increase the involvement and awareness of the sponsor of the clinical trial. The sponsor, usually a pharmaceutical company, is all but divorced from the clinical trial informed consent process. Correspondence on informed consent issues is usually limited to that between the investigator and the IRB, although it must be noted that some large pharmaceutical companies do provide the investigator with a suggested draft consent form that may be modified according to local customs and requirements. Nonetheless, it is clear that once the IRB/investigator negotiations on informed consent begin, the sponsor essentially takes on the role of
interested bystander—a role more often than not actually appreciated by the sponsor's representatives, especially when IRB review and approval progresses smoothly.

The sponsor's lack of involvement in the clinical trial informed consent process is customary not only because of the ease with which the activity is delegated to the investigator. In addition, the FDA actually encourages sponsor non-involvement in the clinical trial informed consent process. Of course, such policy is designed to maintain IRB approval on the local level and simultaneously prevent the sponsoring company from inappropriately entering the discussions. In this regard, such policy is appropriate in its basic philosophy. However, this attitude neglects to appreciate the legitimate input available from the sponsor on the issues.

The sponsoring company is actively involved in every other facet of the clinical trial, from its financial aspects to assisting in writing and editing the manuscripts. Further, sponsor representatives, usually referred to as Clinical Research Associates (CRAs), monitor the progress of the study at frequent intervals. During these visits, the CRAs assure the integrity of the data by verifying that the protocol is in every respect being followed. The CRAs also verify that signed informed consent documents are being obtained for all clinical trial subjects.
Certainly, it is not unreasonable to expect the sponsor to take a more active role in insuring that the ethical parameters of the protocol and entire research project are implemented. This type involvement can come in the form of informed consent consultation, or perhaps actually monitoring the informed consent process. Rather than merely check to see that appropriate consent forms are signed, the sponsor research representatives can actually, via an ongoing monitoring process, help validate that a legitimate clinical trial informed consent process has been observed.

The primary advantage of sponsor involvement is that all parties in the clinical trial are thus brought into the informed consent process. Thus the resources of the sponsor, which are always greater than those of the investigator, may be effectively utilized in an effort to insure a more valid process of clinical trial informed consent.

Justice in the paradigm

Another suggestion for improving the clinical trial informed consent process is to insure justice in the paradigm. Unfortunately, clinical trial subjects do not represent a broad cross section of society.¹⁶ There is an overrepresentation of the poor, minorities, and less
educated.¹⁶ One cannot assume, however, that these groups are necessarily singled out for research exploitation. A more likely explanation, actually, is that most clinical trials are conducted at major metropolitan medical schools and hospital facilities—institutions that are more often than not located in the inner city. Thus an argument could be made that propinquity rather than exploitation is the principal reason that the less advantaged members of society are found in disproportionate numbers in clinical trials, since these individuals generally live in these same areas. Further, for economic and other reasons, the inner city university or public clinic is also the only readily available health care facility for them. This distinction between propinquity and exploitation is not absolute, as one must be mindful of the fact that propinquity may indeed be the breeding ground for the exploitation of these very groups.

Regardless, however, of whether exploitation is present, there is a clear warrant for justice in clinical trials. Distribution of the benefits of medical research theoretically invites a just distribution of research risks, although, as I argued in Chapter three, this is probably an unrealistic goal. In fact, since clinical research participation is driven primarily by economic and access concerns,¹⁷ one cannot demand or even expect there to be a
broad representation of races and social classes in such projects. Rather, the focus must be on justice in the background institutions, rather than in the strict distribution of research risks and burdens.

Earlier, I argued for the appropriateness of Rawls’ thought in forging a more valid clinical trial informed consent paradigm. Consistent with the notion of the priority of background forces and structures in the paradigm, the utility of Rawls’ thought in this regard is less from a distributive standpoint, and more one of insuring just background institutions.

The background institutions in the clinical trial informed consent paradigm are numerous and complex. Health care delivery, allocation of resources, and provider-patient relationships cannot be changed overnight. The impracticality of implementing major changes in these institutions does not provide the grounds for ignoring the issue. A first step is an awareness of the existence of background issues in clinical trial informed consent, as opposed to concentrating on the individual consent transaction.

My emphasis upon the priority of justice in the background institutions does not obviate the need to address justice in a given clinical trial. That there is an over-
representation of minorities and the poor in clinical trials is problematic only if this unequal sharing of research burdens is not justified by acceptable standards or norms. The voluntary nature of clinical trial participation is one such rationale, albeit weakened by the fact that the "voluntary" status of participation may in many cases be questioned. Further, one could argue that the benefits of clinical trial participation, e.g., compensation and a higher standard of care, outweigh the research burden for a given individual. However, as Karen Lebacqz has cogently argued, benefits do not necessarily outweigh the risks associated with research participation—risks that indeed may not be fully understood by the sponsor, investigator, or subject.

Lebacqz also notes that ideally those persons who have borne the burdens of research should be the first to reap its benefits. However, Lebacqz asserts that it is "probably impossible" to require that individuals who participate in medical research be the first to enjoy the benefits of breakthroughs derived from their participation. Rather, Lebacqz calls instead for a system in which "justice may be applied in its social aspect here: the class of research subjects in general should be among the first to receive benefits of new therapies."
Actually, the ideal situation Lebacqz describes, in which the participants individually reap the benefits of medical discoveries, is not as utopian as she appears to think. A common addition to clinical trials in the United States is the "open-label extension" of the core protocol. Under such an arrangement, subjects who have done well during a clinical trial of an investigational agent may be maintained on that agent for periods of time up to the marketing approval of the compound. Such extensions, usually in Phase III trials, require the prospective approval of the FDA, but this is usually granted. All costs of treatment are borne by the sponsor, who obtains virtually no efficacy data from the extended protocol. Very little is required of the subject, other than monthly or bi-monthly assessments for safety data. Of course, one obvious disadvantage to the notion of an extended protocol is the fact that subjects who were on placebo cannot participate, as the efficacy and dosage of the investigational agent is unknown in such individuals.

Conclusion

As stated in Chapter one, the basic argument of this dissertation is that the theologically trained medical ethicist is uniquely qualified to address the issue of clinical trial informed consent. In support of this
argument, I have offered an analysis of what I claim to be the paradigm of clinical trial informed consent—a paradigm that, because of its essential function of recruiting outsiders into the realm of human experimentation, is significantly different from the notion of informed consent for medical treatment.

My analysis has demonstrated that reflection on the paradigm category of recruitment points to the notion of basic fairness in the institutional structures and forces at work in the clinical trial informed consent process. The transaction between the investigator and the potential subject does not occur in a vacuum. Rather, basic structures such as health care delivery systems, physician-patient relaationality, and the regulatory role of government are intermingled in a matrix structure that can produce a situation contrary to the true spirit of clinical trial informed consent.

Similarly, the paradigm category of "outsider" has pointed to the need for recognition of the potential clinical trial subject as a stranger to the medical system in which he or she is posited. The actual clinical trial informed consent process and transaction between the investigator and the potential subject must not be appreciated merely in terms of interaction between competent adults. The lack of a "medical identity" in the clinical
trial places the potential or actual subject in a position that invites close scrutiny to insure that coercive and overly persuasive influences are left out of the process.

Finally, the paradigm category of human experimentation has pointed to a lack of appreciation for the experimental status of clinical research. My analysis has demonstrated that it is not the experimental nature of the compound being tested that warrants such status, but rather the protocol of the research project itself. The research protocol disallows any of the customary treatment boundaries found in the physician-patient relationship. Failure to recognize and appreciate this distinction easily leads to the viewing of the clinical trial as an extension of the treatment model. Further, the human experimentation element of clinical trials must be addressed in an effort to prevent subjects from being treated merely as means to an end.

The paradigm categories thus collapse around the issues of institutional forces and care for the stranger, with the human experimentation category pointing to the need for corrective action. I have suggested that the thought of John Rawls and Paul Ramsey, with their respective views on society's basic structure and the notion of care, may be correlated with these paradigm categories. The validity of the thesis itself rests upon this claim of a correlative relationship--a relationship that has been demonstrated to
exist between the respective thought of these two scholars and the clinical trial informed consent paradigm categories in a Tillichian correlative fashion, and not just from the perspective of "applying" the thought of Rawls and Ramsey to the issue at hand.

The theologically trained medical ethicist thus possesses the ability, via the correlative influences of Rawls and Ramsey, to address the realities of the major elements of the clinical trial informed consent process.
EPILOGUE

In addition to demonstrating that the theologically trained medical ethicist is uniquely qualified to offer guidance and insight into the notion of clinical trial informed consent, this dissertation has also made the following more broadly based contributions that should be noted:

1) Provided a conceptual framework for correlative applications of theological and philosophical answers to questions of meaning, significance, and value—contingencies that are frequently faced by the medical ethicist.

2) Argued for the appreciation of a separate paradigm for clinical trial informed consent as opposed to treatment informed consent—an appreciation that can lead to more in-depth analyses of other important questions that demand the recognition of differences between medical research and practice.

3) Expanded the health care applicability of John Rawls' thought. Rather than relying upon rights-based claims, which is usually how Rawls' thought is introduced in health policy related issues, the dissertation has focused on Rawls' notion of the basic structure of society.
4) Exceeded the call of Shelp, MacIntyre, and others for dialogue between the disciplines of religious studies and medical ethics. The dissertation has argued that not only should the theologically trained medical ethicist be included in discussions on clinical trial informed consent, but that such individuals offer a unique interpretive perspective in such affairs.
Endnotes to Chapter four


4Basic Christian Ethics, p. 148.

5Ibid., p. 114.

6The Patient as Person: Explorations in Medical Ethics.


8The Patient as Person, pp. 1-58.

9"Informed Consent in Research and Practice," p. 1230.


12Ibid.


16Ibid.


19Ibid.

20A similar, but less formal, arrangement is the "Treatment IND."
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