

Ethos and Regula in Contemporary Clinical Research

by

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ABSTRACT

With new trends in drug development and testing, it must be determined whether the current state of balance of ethos (the moral norm) and regula (the legal framework) can successfully protect patients while keeping the door to scientific innovation open. The rise of the Clinician Investigator (CI) in both academic and private research introduces a challenge to the protection of subjects in the conflicting dual role of physician and scientist. Despite the constant evolution of regulation and ethical standards, questions about the roles' combined effectiveness in relation to this challenge persist. Carl Elliot describes the suicide of a patient-subject enrolled in an industry-funded physician-run anti-psychotic pharmaceutical drug trial in a 2010 *Mother Jones* article. Elliot provides a personal account of discrepancies seen in the ethical principles of beneficence, respect for subjects and justice. Through analysis of the problems presented in the case as a model for potential dangers in clinical research, the effectiveness of ethics and law in protecting human subjects is examined. While the lag between ethical standard and regulation has historically shown to cause similar issues, the misconception of current regulation and ethical standards may be contributing to the decrease in subject protections. After IRB approval of subject protections in the research protocol, CIs have been shown to downgrade their responsibility to maintaining ethos through the course of the trial. And, despite their experience in patient-centered ethos as a physician, CIs may be inclined to substitute these values for the ethos of a researcher, with the goal to avoid therapeutic misconception. Maintaining personal responsibility for subjects beyond regulatory

structure, and promoting the welfare of the subjects in regards to the ethical standard of research investigators, will provide added security for subjects and decrease opportunity for exploitation in future research.

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Chapter 1

INTRODUCTION

There is a complex relationship between medicine and scientific research. In our health-driven society, one cannot exist without the other. Declines in physical and mental well-being cry out for biomedical solutions. In response, research is conducted by both academic institutions and private firms to develop therapies and to determine the success of these innovations. This circle continues as research uncovers more information about the human function and its reaction to internal and external stressors. Maintaining a balance between medical practice and research is crucial in continuing the pursuit for better health outcomes and the well-being of society. If health is declining at a pace much quicker than the development of therapies, individuals will not have access to the proper biomedical interventions and, as a result, will fall victim to a broad range of health conditions. To keep up, researchers must strive to pinpoint the origin of diseases and conditions leading to declines in health and understand their functioning in order to start the search for a therapeutic intervention.

A similar relationship exists between ethics and the law. Morals and social values create a shared sense of what is good and what falls short. Consensus on these principles helps to create a framework on which the society can exist and, hopefully, thrive. As new members are added to society, this structure can provide guidance to morals and values that are able to be adopted. However, a cyclic pattern does not always exist between the ethics and law. A consensus on value does not always result in the formation of legal structure. And, on the other hand,

the existence of a regulation may not reflect the consensus of morality in the society. So, despite of the connection existing between ethics and law, the two may appear as separate bodies of structure and this has potential for discrepancy between the goals and outcomes of each. Wavering in the relationship of ethics and law has the potential to create conflict when developing structure amongst other cyclic relationships, such as that of scientific research and medical practice.

The purpose of this study is to better understand the ethics and regulation surrounding clinical research in the constantly evolving medical field. With the addition of new challenges in drug development and research, it must be determined whether the current state of balance of ethics and law can successfully protect patients while keeping the door to scientific innovation open. The challenge presented in this case focuses on physicians acting as research investigators. These ‘clinician investigators’ have to balance the conflicting duties as a physician and a scientist in order to pursue involvement in clinical research. Although layers of regulation have been added to protect human subjects in response to challenges in research over the years, a potential for gaps in protections continue exist and can lead to the unnecessary harm of the participants. It needs to be determined whether the combination of value systems and the current regulatory system, for both physicians and researchers, is capable of supporting the protection of human subjects in clinical research. If not, discussion of the duality of the clinician-investigator role may shed light on how to proceed with clinical research of this nature.

1. The Rise of the Clinician Investigator

Two distinct roles have been established in clinical medicine: the scientist and the clinician. On one hand, scientific investigators work at the front end using past knowledge and experimentation to advance their field. They work to expand the boundaries of science, particularly medical science, from the lab bench. Their goals tend to focus more on knowledge expansion than on health of individuals enrolled of their research. On the other hand, clinicians apply the science through the work of diagnosis and treatment. Their focus has been on therapeutic beneficence toward individual patients. Their work toward advancing health has created a caring, humanitarian persona, but may not appear to understand the scientific under-workings of their career. Although these roles appear distinct, they are dependent on each other for successful health outcomes. Scientific knowledge is necessary to create new diagnosis and treatment techniques and the physician-patient relationship is necessary to apply these techniques to increase the health of patients. Therefore, the separation of these roles may not be the most efficient in creating new health knowledge and better health outcomes.

Recently, the joining of the roles of physician and scientific investigator has been encouraged as a means to advance progress in both the scientific and medical communities. The goal is to develop a person who can both advance science while improving the health of individuals. This ‘knight in shining armor’ of sorts is the Clinician Investigator (CI). A CI is a physician who also acts as a scientific investigator through producing scientific research and conducting clinical trials in their field of practice while still treating patients (Lader et al.

2004). This person can go back and forth between the bench and the bedside and can foster basic research into clinical settings of practice. Also, he or she can take clinical research and make it more relevant to applied clinical trials. Although the CI may seem to connect these previously distinct roles effectively and efficiently, there exists a concern in attempting to balance the traditional goals of the physician and the scientific investigator (Miller, Rosenstein, and DeRenzo 1998; Gorski, 2009). The culmination of trying to advance science while ensuring therapeutic benefit creates an ethical challenge, and potentially a conflict of interest, for the CI.

2. From Academic Medical Centers to Private-Sector Research

Research universities classically have been associated with CI research. The academic setting provides physicians with the support needed to conduct extensive clinical trials. Also, the presence of science departments alongside medical centers allows for streamlined transfer of information. The US and Canada have made attempts to fund more CI's through the development of MD/PhD programs, which make medical training programs more flexible with scientific exploration (Goldstein and Brown, 1997; Morin et al., 2002; Culotta, 1993). These programs allow medical candidates to become exposed to research methods in the academic setting, which creates a starting place for CI pursuits. Also, all medical research is developed and executed under the regulation and approval processes of trusted university IRBs. This setting creates an ideal for the conduct of CI research.

To manage the financial burden of research with the goal of maintaining steady profits, pharmaceutical companies are developing new strategies for cost-efficient research. Recently, there has been outreach by corporate research sponsors toward private-sector physicians to pursue academic research in their clinical setting (Morin, Rakatansky, Riddick, et al. 2002). Specifically, the use of private-sector research was shown to increase by three times previous spending in the 1990s and is still on the rise (Cockburn, 2004). The physicians provide expertise and interest in the field, as well as pools of potential research subjects (Klein and Fleischman, 2002). This arrangement has the potential to be financially beneficial for both the pharmaceutical company and the contracted physician. The physician can gain access to additional salary while the pharmaceutical company can hope for success in research and development of new drugs to cope with recent patent expiration.

Motivations for involvement in research, as a private-sector physician, go beyond financial compensation. There is a general consensus that research is inherently good for all involved because it assists in the expansion of scientific knowledge (Klein and Fleischman, 2002; Lader, 2004; Snyder and Mueller, 2008; Boyd, Cho and Bero, 2003). The expansion of knowledge can lead to the fulfillment of the individual physician's academic goals, which may not commonly be available in the setting of private practice (Klein and Fleischman, 2002). These academic goals may include not only the completion of research, but the ability to publish work and get academic credit for their participation (Lader, 2004). When becoming involved in research, the physician may have the

opportunity to receive more education about the drug through discussion with those involved in pre-clinical development of the therapy. This education could include participation in scientific sessions to learn more about the issue at hand or to present results after the course of the trial (Lader, 2004). Also, the opportunity to take part in research trials could add to the prestige of the practice or institution participating in research (Lader, 2004). The physician would be able to associate his/her practice of medicine with the cutting edge medical technologies currently in development, which could lead to positive reviews and potential increase in patients. Finally, by participating in research, physicians have the opportunity to improve the health of their current patients. Through the use of the most state of the art pharmaceuticals and devices, they would be able to provide the best health care, the primary objective of medical practice (Snyder and Mueller, 2008).

3. Discrepancy in Conduct

Primary care physicians enrolling patients in clinical trials causes a new set of ethical concerns, which vary from clinical research ethics and physician-patient conduct alone. And, unlike the academic CI, the private practice physician may not have clinical research training or experience. Although physicians undertaking research and caring for patients may both conduct their craft for the overarching goal of harm avoidance, the motivations are different (Brody and Miller 2003). Research, unlike clinical medicine, does not include a duty to promote therapeutic benefit and, thus, the blurring of these career paths has the opportunity to cause miscommunication with patients in their role as research participants, as well as

internal moral struggles for the CI. While facing these challenges, it must be determined whether the attempts to balance these two roles as one individual is the most ethical and efficient way of advancing science (Bloom 2003).

Steps have been taken to evaluate the role of the CI in the both the academic and private practice setting. This duality creates ethical concern, both for the patients enrolled in the study and the physician acting as investigator, and this is expressed throughout the literature. However, with sufficient focus on informing the physician of the research properly and informing the participants of not only the trial but also the special role the physician has assumed, participants can be protected and significant progress in research can be made (Klein and Fleischman, 2002). With multiple credible sources releasing proposed action in moving forward with research, progress toward making changes to include proper protection would seem expected.

However, in a 2008 study, Fisher described that physicians contracted for private (for-profit) research do not feel personally responsible for the protection of their subjects (2008). The trial protocol, designed by the pharmaceutical company, includes informed consent component to be discussed with the enrolling participants. Information includes the purpose of the trial, the process of the trial, the risks and benefits from the therapy, and other pertinent information (Rogers and Schwartz, 2002). This component, along with the protocol as a whole, is reviewed by an Institutional Review Board prior the beginning of any human subjects research. The IRB, a private company hired by the pharmaceutical company in this case, determines whether the risks have been

minimized and benefits appear to outweigh risk involved, along with other features for protecting participants while advancing science. Since this process is reviewed by the drug's developers as well as a committee whose job is to protect patients, some physician-investigators feel that all unwarranted risks have been accounted for and the trial has been deemed ethical and can be carried out without further analysis (Fisher, 2008). A discrepancy exists between the role physicians play in the ethics of the trial and their perception of participant protection. It is possible that progress in protection of subjects in for-profit CI research through legislation is not being made despite the in-depth conversations occurring in the ethics community.

4. Research Question

The remainder of the thesis is directed toward answering the following question: Given duality between research and clinical care, how do we balance ethos and regula to lead to good outcomes for participant/patients?

Chapter 2

ETHOS AND REGULA: ETHICS AND LAW

1. Definitions

Ethos is one of Aristotle's three modes of persuasion. Ethos refers to the character of the speaker, whose intent is to portray credibility through fair-mindedness (Aristotle, 1991 in Constantines, 2001). To appear credible, one must express practical wisdom, virtue and good will. Although ethos is a term of rhetoric, it has been adapted to social norms of modern science and be used as a tool to foster discourse (Constantines, 2001). The arena of science creates a unique environment for the development of ethos. Robert Merton has categorized scientific reasonableness into four norms: universalism, communality, disinterestedness, and organized skepticism, (Merton, 1989 in Constantines, 2001). Bernard Barber added a fifth norm, ethical neutrality (Barber, 1952 in Wunderlich, 1974). These norms work as platforms for developing perceptions of ethos. Merton explains, "[the] ethos of science is that affectively toned complex of values and norms which is held to be binding on the man of science. The norms are expressed in the forms of prescriptions, proscriptions, preferences, and permissions. They are legitimized in terms of institutional values... [The ethos of science] can be inferred from the moral consensus of scientists..." (Merton, 1989 in Constantines, 2001). Ethos today is expressed in the form of ethics codes and recommendations of institutions and nations, as well as in mutual discourse between professionals and scholars. These norms work to serve the well-being of

the community and the individual to the community's standard of the morality. Continued discourse on ethics help to better shape these norms as science progresses.

Although the ethos may be seen as a standard in a society, *regula*, Latin for 'rule', dictates legal obligations (Du Plessis, 2010). Changes in *regula*, also referred to as regulations and laws, are determined by the governing body. *Regula* often encompasses the moral standards of the society. However, all *regula* does not necessarily reflect these judgments and may even conflict with the ethos. In science, the regulations governing research and treatment have worked to incorporate the discussion of ethics, but discrepancies have been present over the course of its history.

2. Ethos and Regula in Human Subjects Research

Human subject research has been practiced as medicine has evolved. But, it was not until revelations about the treatment of subjects after the end of the second World War that catalyzed ethical discussion of its practice. With news of exploitation released through journalism, the necessity for change in research conduct was obvious (Rothman, 1987). The *Nuremberg Code* was established in 1949 as a response to the Nazi War Crimes Trials involving abuses through human experimentation. This code encouraged that consent by all human subjects research should be voluntary, hoping to avoid cases of exploitation as witnessed in World War II. Also, it expressed that participants should be free to discontinue taking part in a trial at any point. In addition, the concepts of determining a

favorable risk-benefit ratio and justifying the potential risks were introduced to the discussion of research ethics.

The World Medical Association released the *Declaration of Helsinki*, an international guideline for human subjects research ethics based on the *Nuremberg Code*, in 1964. This code took the principles given in Nuremberg and correlated them to the standard duties of physicians, creating relevance for research in pursuit of research with therapeutic objectives. Since its release, it has been noted as the most significant document in the development of human subjects research regulation (Rothman, 1987). It has been revised six times since its release, the most recent being in 2008. *Helsinki* became the overwhelming standard among practitioners, creating a universal baseline for ethics discussion and a foundation for later regulation. The *Declaration of Helsinki* was based on the fundamental principle of respect for the participant. This respect created a need for informed decision-making regarding enrollment. Also, it set precedence for protection of the subject from harm over opportunity for scientific gain.

Driving the provisions were ongoing instances of human exploitation and unfavorable risk-benefit ratios. Prominent in the release of this information was Henry Beecher, a research professor at Harvard Medical School. In a seminar article published in *The New England Journal of Medicine*, he presented twenty-two examples of misconduct in human subjects research spanning various disciplines of medicine (Beecher, 1966). This information not only surprised readers, but also showed that exploitation in research was happening despite the introduction of ethical codes to promote participant protection. The impact of this

information eventually resulted in the development of more detailed structures for informed consent as well as the formation of institutional review boards (IRB) to oversee research of this nature (Rothman, 1987). But Beecher, by contrast, was especially concerned to reinforce the ethos of medicine as a core element of conscientious research.

The public awareness of flaws in human subjects research was at an all-time high with the exposé of the Tuskegee Syphilis Trials. In this experiment, black men of low socioeconomic classes with syphilis were left untreated in order to learn about the course of the disease. At the time of the trial, a standard medication was available and approved for the treatment of syphilis (Heller, 1972; Jones, 1981). A national panel was appointed to review this case and it was determined that current standards for research ethics were inadequate. The risk of this experiment is obvious, and the Tuskegee syphilis experiment is widely interpreted as blatantly exploiting members of vulnerable socioeconomic classes and racial groups. The lack of participant protection through subjecting participants to avoidable harm while exploiting their racial and socioeconomic backgrounds proved that change needed to continuously be made among regulation of human subject research. Since Tuskegee came to public attention, the treatment of human subjects participating in biomedical research has been regulated and overseen federally and through individual institutions with the additional of supplementary codes. An evolving modern standard understanding of clinical research ethics has provided grounding to evaluating the dynamic nature of biomedical research under the framework of clinical research ethics.

3. Current Regula

i. *45 CFR Part 46*, Department of Health and Human Services, 1991

This regulation is the primary set of Federal human subjects research protection regulation in the United States, adopted in 1991. Also referred to as the Common Rule, this legal code applies to federally funded human subjects research and sets forth the legal standards and requirements for the conduct of covered human subjects. All research subject to the Common Rule is required to follow specific guidelines for obtaining independent review by an institutional review board and informed consent for subjects. The research undertaken with government funding must comply with the Common Rule's requirements.

All human subjects research is to be reviewed by an Institutional Review Board (IRB). The specifics of IRB constitution are stipulated by the Common Rule; an IRB must have a minimum of 5 members representing a diversity of expertise, including members affiliated with and members independent of the institution in which the protocol under review will be undertaken. The purpose of the IRB is to review proposed human subjects research to protect the safety and interests of the human subjects. IRB approval relies on the requirements that the project minimizes risk to subjects, the potential risks are reasonable in the scope of anticipated benefit, the selection of subjects is justified, and informed consent is both substantial and properly documented. Approval can be granted with or without revisions or the project can be rejected. All research approved by IRBs is subject to ongoing oversight by officials of the institution at any time.

Specific requirements are signifiers of the ethical requirements of informed consent. The baseline elements are as follows: explanation of the research, expected duration of participation, description of the protocol, identification of experimental portions of protocol, potential risks to individual, anticipated benefit of trial to individual and/or society, list of alternative procedures available, statements concerning confidentiality, compensation for injury, and available procedures for case of injury, contact information for further questions and in case of injury, statement of voluntariness of participation, and statement of ability to withdraw. The following elements may be necessary for inclusion based on the research at hand: potential for unforeseeable harms, cause for termination of the subject's participation by the investigator, additional costs of participation, consequences of withdrawal from study, disclosure of new information as study progresses, and the size of the study. Waiver or alteration of informed consent requirements may be granted by the IRB when research includes the following: potential for no more than minimal risk, information that can affect welfare of subject, and when informed consent would disturb the validity of a study. Documentation of informed consent must be signed by the subject or legal proxy on the IRB-approved form, with a copy made for the subject. In cases of oral presentation of informed consent, a shorter version of the document is to be signed by participants and a witness of the oral presentation. Signatures may be waived in cases of potential for confidentiality breach or when research presents no more than minimal risk, which is similar to standard medical procedure.

ii. FDA Regulation

The Food and Drug Administration continuously is updating their regulations to reflect Congress's laws pertaining to the products the FDA regulates (FDA, 2012). The organization translates the laws through drafting proposals, which are scrutinized internally and by the public before becoming enacted. This process creates an opportunity for feedback and improvement on the policies of the FDA. The resulting regulation is applied to all FDA sanctioned research and is filed under the *Code of Federal Regulations Title 21 (Food and Drugs), Chapter 1 (Food and Drug Administration)*. Clinical research legislation includes the responsibility of IRBs and the details of informed consent procedure.

All research is to be reviewed by an IRB prior to conducting the clinical portion of the trial and throughout its course (*21 CFR 56.103*, 2011). As in *45 CFR Part 46*, the IRB must consist of at least 5 members, of both science and non-science backgrounds. Creating a diverse group of individuals, intellectually and based on other personal characteristics, works to promote the welfare and protection of the diverse population of subjects participating in the research (*21 CFR 56.107*, 2011). Each IRB must register with the FDA prior to participating in regulatory duties (*21 CFR 106*, 2011). These duties, as stated in *21 CFR Part 56.109.a*, are to “review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities...” (2011). Evaluation of the research includes review of any risks to the subject, the reasonableness of said risks to anticipated benefits, and fair subject selection (protection of vulnerable groups) (*21 CFR 56.111*, 2011). The IRB is to continuously monitor the study in

order to maximize safety and confidentiality of the subjects, where applicable. This approval also requires that subjects be provided with sufficient informed consent prior to participation, with the only exceptions being minimal risk, procedures that do not require consent outside realm of research, and sanctioned emergencies (*21 CFR 56.109.c*, 2011). All approval can be suspended or terminated secondary to, but not limited to, cases of unexpected serious harm to research subjects (*21 CFR 56.113*, 2011).

Informed consent is expanded upon in *21 CFR Part 50*, which addresses the protection of human subjects (2011). The process of informed consent is to provide the subject with substantial information to make a decision of whether or not to participate while minimizing instances of coercion and outside influence (*21 CFR 50.20*, 2011). This document prohibits waiving the legal rights of the participant as well as the legal responsibility of the investigator and related parties. The ‘basic elements’ of the informed consent are as follows: (a) statement of the project, procedure, and that research is experimental, by nature, (b) foreseeable risks, (c) reasonably expected benefits, (d) alternative treatment available, (e) statement of confidentiality, and (f) availability medical care provided in instances of harm. It may also include, among other items, one or more of the following: (a) statement of unforeseeable risks, (b) potential termination on behalf of the investigator, and (c) consequences from terminating trial prior to completion (*21 CFR 50.25*, 2011). A physical manifestation of these elements is to be signed by the subject or his or her legal proxy, with copies kept by both the subject and the investigator (*21 CFR 50.27*, 2011).

4. Current Ethos

i. Moral Norms for Practitioners

a. The Hippocratic Oath

The Oath of Hippocrates is a Greek text recorded 400 BCE that continues to be sworn, in some form, by physicians professing to practice medicine ethically (North (trans.), 2002). It is commonly seen as a rite of passage for those students becoming practitioners. Its original text professes that one shall swear by the oath in the practice and teaching of medicine. It expresses need for patient protection by the physician, stating that one shall “do no harm or injustice to them.” (North (trans.), 2002) The translation also states that the physicians shall practice “regimens which will benefit [their] patients according to [their] greatest ability and judgment” (2002). These statements affirm both beneficence and non-maleficence in the practice of medicine.

Although it is still used in some form today, the original text does not encompass all aspects of today’s medicine. Modern derivations, which have removed portions of the original and added portions regarded as more relevant, are also recited and referenced when addressing medical ethics (Antiel et al., 2011). A widely used 1964 version addresses beneficence and non-maleficence in practice similar to that of the original text. It also addresses modern ideas of patient care. Bedside manner is included as follows, “I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug” (Lasagna, 1964). It

creates a sense of humanity in the practice of a science. The humanity of the patient is also mentioned, noting, "... I do not treat a fever chart, a cancerous growth, but a sick human being" (Lasagna, 1964). Through the eyes of this humanity, physicians will face decisions of life and death, which this modern version suggests should be handled with thoughtful personal judgment.

b. American Medical Association – Medical Ethics

The American Medical Association's (AMA) Code of Medical Ethics provides physicians with a standard for upstanding behavior in the medical profession. This code serves to illuminate the ongoing responsibilities physicians have toward their patients, society, members of the field, and their own self (AMA, 2001). The AMA set forth a series of nine principles to act as a core of ethics in medical practice. Although these principles are not legally binding, the AMA holds that "ethical obligations typically exceed legal duties" (AMA 1.02, 2001) – in other words, *ethos* exceeds *regula*. Acting within the law does not ensure ethical judgment and practice. Thus, physicians must ensure that justice is upheld as dictated by ethics, even when current regulation may conflict. And, despite the lack of legal bearing, failure to follow specific duties and obligations set out in this code or instances of unethical conduct may result in disciplinary action, such as suspension or expulsion from the profession (AMA 1.01, 2001). The physician's responsibilities as cited in the principles are as follows: (a) to provide competent care with compassion and respect, (b) to be honest and maintain professionalism to current standards, (c) to act lawfully and to promote

legal change where needed, (d) to respect patients, colleagues, other professionals in the field and their privacy, (e) to continue to study, advance scientific knowledge and to call on knowledge of other professionals when needed, (f) to have freedom to choose who to serve, who to work with, and where to work (in non-emergency cases), (g) to participate in the betterment of community health, (h) maintain responsibility to patient as forefront in all practices, and (i) provide health care access to all people (AMA, 2001).

A physician-patient relationship arises when a physician works to meet the medical needs of a patient. By AMA opinion, this relationship is based on mutual trust and creates an ethical obligation the physician has toward the patient (AMA 10.015, 2001). This obligation is to place the patient's welfare above all else during the course of the relationship, including above institutional and physician self-interest. This is achieved through using sound judgment to make medical decisions while upholding the interests of the individual patient. These interests are protected through providing patients with a right to making health care decisions independently based on knowledge of the procedure, with guidance from the physician, and in confidence to maintain privacy. Beyond respect and dignity, the patient also has the right to timely attention to and care of his or her health, based on the needs presented. The physician must preserve these obligations until the patient no longer is in medical need, the patient discontinues the relationship, or the physician coordinates continued care elsewhere. The physician may not discontinue care if treatment is still medically necessary for the health of the patient (AMA 10.01, 2001).

The patient is also a key part to successful physician-patient relationships and must take an active role in the betterment of their own health (AMA 10.02, 2001). While the physician has duties to provide care, the patient has the responsibility to open communication through the decision-making process and treatment course. This includes scenarios in which the patient wishes to revisit medical decisions and reconsider their options. The patient also has the responsibility to comply with the treatment course. These are based on the patient's right to make autonomous decisions, asserting self control in their medical care. In line with informed consent, the patient or their proxy always have the right to refuse medical care.

c. American Psychological Association Ethics

Beyond medicine, ethic standards are established for psychological therapy by the American Psychological Association. The standard of ethics for treatment, as well as research, is based upon a series of five general principles. The principles are in place to guide and encourage psychologists to practice to their professional best, in terms of ethics (APA, 2010). They are not obligatory in nature, but act as inspiration for success in day to day work.

Beneficence and non-maleficence is the first of the five principles. Psychologists should work to benefit their patients while taking the precaution to avoid harms. The protection of their patient's welfare is a direct result of decision making on the part of the psychologist, so this decision making should be made independent of outside influence. Personal influence, such as mental and physical

health factors, should also be assessed, as it can also affect the welfare of those treated (APA, 2010).

Fidelity and responsibility make up the second principle. Psychologists have both scientific and professional responsibilities to those they work with. All conflicts of interest and opportunities for exploitation are to be managed. It is their obligation to uphold these standards and maintain trust within the relationships established (APA, 2010).

The third general principle is integrity. As stated in the APA's Ethical Principles of Psychologists and Code of Conduct, "Psychologists seek to promote accuracy, honesty and truthfulness in the science, teaching and practice of psychology." (APA, 2010) They are to not engage in activities that would compromise the health of their patients or the accuracy of research. In cases where deception is ethically justifiable, it is the responsibility of the psychologists to understand consequences and mistrust that may evolve and correct these problems to the best of their ability (APA, 2010).

Justice is the fourth of the general principles. All persons are entitled to access to and benefit from the progress of the field. Psychologists must promote this through managing biases in practice and research and understanding limitations, both personally and of the field (APA, 2010).

Wrapping up the five principles is respect for people's rights and dignity. "Psychologists respect the dignity and worth of all people, and the rights of individuals to privacy, confidentiality, and self-determination" (APA, 2010). Special considerations should be taken into account to ensure autonomy for

varying levels of vulnerability. They must take into account their patient's culture and individual characteristics, such as age and gender, and work to eliminate any bias stemming from these factors. Prejudice is not condoned (APA, 2010).

In terms of therapy, psychologists must obtain informed consent for the course of treatment. This process should include information regarding the treatment, risks involved, alternative course of therapy, any fees in place, and the involvement of third parties, if relevant. Also, the limits of confidentiality between the psychologist and patient are to be explicitly defined. Sufficient time to ask questions or state concerns is to be given to the patient or third party prior to beginning therapy (APA, 2010).

Ethical consideration also applies to the termination of therapy. The psychologists can terminate the therapy if it is shown that the patient is no longer in need of the service, no longer is benefiting from it, or if harm is probable if the therapy is continued. Psychologists can also terminate therapy when they feel endangered or threatened by the patient or a person related to the patient. Prior to termination, psychologists are to provide proper counseling explaining the end of therapy and alternative services or providers, if necessary (APA, 2010).

ii. Moral Norms for Researchers

a. The *Belmont Report*, the National Commission for the Protection of Human Subjects in Biomedical and Behavior Research, 1979

In response to the investigation of the Tuskegee syphilis experiment, the US government needed to determine the core principles of human subjects

research ethics and to create a way in which these principles could be executed and protected. The National Commission for the Protection of Human Subjects in Biomedical and Behavior Research was ordered in 1974 via the National Research Act to complete this task (NIH, 1979). By 1979, the commission had created and published the *Belmont Report*, a document highlighting research ethic standards and recommended implementation. Although this document does is not regulatory in nature, it created a baseline for ethic discussion and the development of regulation.

Section 1

The first section of this document differentiates the “boundaries between practice and research” (1979), defining and distinguish the variance in the goals of research and practice. Medical practice involves actions to enhance the well-being of the individual and has expectation of successful therapeutic benefit. Medical research involves actions to test a hypothesis with a rigid protocol to expand upon current knowledge of the field, without expectation of therapeutic benefit of the subject. Straying from medical standards of practice does not always constitute experimentation. Practice of innovative techniques can be handled on an individual basis. However, in more extreme cases of innovation, a formal experiment should be recognized and regulation of this process should be followed.

Section II

The second section of the *Belmont Report* set forth three basic ethical principles to support and structure all succeeding regulation of human subjects research. Justification of all human subjects research should be based upon: respect for persons, beneficence, and justice.

Respect for persons recognizes that humans are autonomous beings and should be treated as such. Autonomous persons are capable of rational and reasonable thought and their interest in self-determination should not be compromised when participating in clinical trials. In cases that autonomy is diminished, individuals should be protected from exploitation. Based on varying levels of maturity and rational capability, protection should be awarded appropriately. These cases should be assessed individually based upon the potentials for risk and benefit prior to proceeding.

Beneficence ensures well-being is protected during the process of clinical research. Two rules have been formulated to address beneficence. The first is that potential harms to subjects should be minimized. The second is that the study's expected benefits should exceed the potential harms. This principle marries the ethos of the Hippocratic Oath with the field of research. In addressing risks and benefits, the research can be better defined and the goal is more likely understood by participants and the public.

Finally, justice defines how the burden of participation and distribution of knowledge must be equalized in order to justify research with human subjects. As seen in previous cases of misconduct in research, such as the Tuskegee Syphilis

Trials, the risk often falls on populations of low social classes while high classes reap the benefits of the treatments developed. Justice can be balanced based on need, effort, societal contribution, merit, and other qualities. The choice should exercise fairness and stay consistent for minimized chance for exploitation.

Section III

The third and final section of the report states how the three aforementioned principles should be applied to current regulation. Three conditions are highlighted: informed consent, risk/benefit analysis, and participant selection.

Informed consent aims to respect the autonomy of all patients by allowing them to determine whether to participate in the study. Information about the trial is provided to the individual, informing them of not only the protocol, but research goals, any risk involved in participating and alternatives to participating. Patients also are to be informed that they can withdraw from the trial at any time. Any information pertinent to the trial should be disclosed at all times, allowing the participant to get truthful information as well as truthful answers to questions asked. Patients should also be properly debriefed, providing any available research results. Informed consent also hinges upon the participant's comprehension of the information provided. Comprehension helps to protect the autonomy of the patients. In cases of increased risk, ensuring comprehension becomes more important and testing the absorbance of information could be helpful. Based on the information given and processed by the patient,

voluntariness in participation is the final piece in protecting the autonomy of the patient. The informed consent process should be executed in a way that does not coerce the participant to enroll. Offers of unfit reward or the exaggeration of benefit is not permitted. The influence of others involved in decision-making, such as relatives, should be monitored as well to protect the participant.

Assessing the risks and benefits of the trial provides information for IRBs about whether the research can be justified and beneficence be maintained. The term ‘risk’ refers to the probability for harm caused by the trial. The range of harm can differ and should be weighted based on the expected severity. The term ‘benefit’ refers to the anticipated welfare resulting from the trial. Benefit from the trial can occur at both the individual and societal levels. Justification of research is possible when risk and benefit is systematically balanced or, preferably, weighted toward benefit. Also, justification should reflect that humans are never inhumanely treated, humans are necessary for the success of the trial, chance for significant risk is justified by potential benefit, vulnerable populations are protected and involved when possible, and all discussion of risk and benefit presented for IRB approval is clearly stated in the informed consent procedure.

Justice in clinical trials is exercised in the selection of research subjects at both the individual and societal level. Individuals as well as societal groups should not be cherry-picked based on favorability or increased ability to exploit. This can help to decrease a burden to participate upon an improper individual or an unfit group. However, the selection of a specific population can be justified if proving to balance risk and benefit, such as choosing adults over children.

Investigators should be aware of any bias (social, cultural, racial, etc.) that may arise during a trial, intentional or not, for biases may skew results in dramatic but also in subtle ways. Institutionalized and other vulnerable populations should not be targeted as sources of participant pools. The decreased capacity to consent based on their surroundings, mental status, and basic needs can easily be influenced and create a potential for exploitation.

b. American Medical Association – Research Ethics for Clinicians

Increasing numbers of physicians, both academic and non-academic, are becoming involved in partnerships with biotechnology and pharmaceutical industry to further research with clinical trials (AMA 8.0315, 2001). The AMA has set out recommendations to assist physicians in maintaining their professional ethical responsibility when they take part in clinical investigations (AMA 2.07, 2001). As noted in chapter 1, there is a duality of purpose in clinical investigation – the research is designed to advance knowledge but tends to be undertaken with patients under clinical care. The AMA recognizes this duality. The clinical investigation is to serve the purpose of producing scientifically valid and significant knowledge within the standards of research. But, despite the presence of the trial, the patient should be given the same attention to their welfare, safety, and well-being as in physician-patient relationships.

In cases of using clinical investigations primarily for treatment, all judgment must be made in the best interest of the patient, as exists in the physician-patient relationship. The patient should voluntarily agree to use an

experimental drug as course of treatment and informed consent process that explicitly states any risks and potential benefits (AMA 2.07, 2001). The physician is required to answer any questions of the patient and provide alternative therapy to the trial. Coercion and exaggeration of clinical benefit should not be used to influence trial enrollment.

Physicians should also be aware of the inherent conflict between the roles of physician and scientific investigator and any additional conflicts of interests. To manage them properly, the AMA recommends that physicians should only participate in trials under their scope of practice (AMA 8.0315, 2001). Additionally, physicians should receive training in responsible research conduct and scrutinize the investigation for subject welfare provisions and scientifically sound protocol prior to agreeing to participate. In cases where patients are subjects, and *vice versa*, physicians should work to illuminate the differences in responsibility of physician and investigator to the patient. It may be appropriate to have someone other than the physician to obtain consent to any clinical investigations. The physician should make sure protocols contain provisions for medical care for participants in the case of complications and should make participants aware of any financial interests the physician has in the research. Finally, the physician should ensure that all data collected be released unobstructed and abnormally delayed by the institution or company they are contracted to.

c. Current Discussion of Research Ethics

The ethical standard for the treatment of human subjects in clinical research extends beyond what is governed by ethical codes and regulation. As seen in the Belmont Report, ethical principles have served as a starting place for the development of both ethical standards and regulation. Informed consent has primarily been thought of as a way to make human subjects research ethical (Emmanuel et al., 2000). But, regulation in this manner does not always incorporate new evolving standards, which are actively discussed by ethicists, physicians, scientists and other academics. Additional principles have been offered to be added to the current requirements for research approval.

The completion of the research should have social, scientific, or clinical value (Vanderpool, 1996 in Emmanuel et al., 2000). Value, in the case of therapeutics, can be referenced to various goals. Value can be found in improvement in health and well-being, the gathering of information that could lead to discovery of therapeutic interventions, and an increase in the knowledge of biological systems (Levine, 1988 in Emmanuel et al., 2000). Research that may take many years may still be justified if goals are reasonable and probable. Projects have opportunity to unnecessarily repeat a previously completed trial or produce results that cannot reasonably be translated into medical practice. It is important to identify value in the research prior to conducting the study because resources necessary for completion are finite and pursuing research with little or no value opens the door for exploitation of participants (Vanderpool, 1996 in Emmanuel et al., 2000).

The protocol of clinical research should be scientifically valid. Social, scientific, and clinical value can be compromised when errors exist in the structure of the project at hand and results are not reliable (Rutstein, 1970 in Emmanuel et al., 2000). Investigators should use their academic background as well as exercise care when developing their protocol to avoid these mistakes (Resnik, 1998). In the comparison of existent therapies, clinical equipoise must be present (Freedman, 1987). Controversy to whether the new treatment is predicted to be more successful than the current treatment needs to exist. Research is not justified if a consensus already exists on the better therapy. Once a scientifically valid research question and protocol exists, changes can be made to the methods to ensure the most ethically favorable participant experience (Emmanuel et al., 2000). Again, this principle can be justified by finite resources and controlling exploitation.

Honesty and openness should be exercised between the investigator and the participant enrolled in the study (Resnik, 1998). The investigator should be sure to give informed consent with all relevant information, including that of risk and potential harm. Also, the investigator should be open and honest about any financial conflict of interest that may exist in the research project. Allowing the participant access to the information will strengthen the respect for the subject as well as allowing them to make the most autonomous decision about their enrollment and participation. Failure to disclose information about the protocol itself, the goals of the project or any reward driving enrollment can lead to exploitation.

Chapter 3

CASE PRESENTATION

As the landscape of clinical research continues to change, it is important to recognize the existing challenges and then determine how they are impacting current cases. The following case falls in the intersection of the for-profit pharmaceutical industry and the rise of the clinician investigator. Carl Elliott interprets a personal account of a case of suicide during an individual's enrollment in an industry-funded physician-run anti-psychotic pharmaceutical drug trial in his *Mother Jones* article (2010). With examples of potential discrepancy in subject protection evidence, but no official findings of wrongful activity, this case presentation provides an interesting platform for evaluating the functionality of ethics in current regulation. This is so even though it is a singular example. And, through analyzing elements of this interpretation on clinical trials, it can reveal sources of lapse in participant protection when physicians assume the role as research investigator and, consequentially, stray away from their norms of care in medical practice.

Note: The following study will be summarized as interpreted by Carl Elliott. Although the study pertains to a real case, the information is presented as a personal matter. Therefore, all information from this case will be analyzed on a hypothetical basis and all discussion will reflect potential for discrepancy in participant protection as inspired by the case, not a critical discussion of the case itself.

A first-episode schizophrenic participant was enrolled in the trial while under medical supervision of Dr Stephen C. Olsen, University of Minnesota Academic Health Centers (UM-AHC). This 26 year old patient had a known history of homicidal tendencies and was noted to be at risk to harm others. Minnesota statute holds that patients who are psychotic and dangerous can be treated without consent due to mental instability or incapability for the course of 14 days. At this time, the patient must comply with the treatment and follow-up instructions by their physician. This either can be done involuntarily through admission to a treatment facility or on an extended-outpatient basis with strict guidelines. The patient opted for this “stay of commitment”. Instead of prescription treatment, the patient was enrolled in a research study. After two weeks of treatment within the confines of the hospital, the patient was placed in a halfway house.

The research study was comparing three FDA-approved “atypical” anti-psychotic drugs, Seroquel, Xyprexa, and Risperdal (the medication originally used to treat the patient after arriving at the health center). This study was comparing the effectiveness of these drugs in first episodes of schizophrenia and was sponsored by AstraZeneca, the manufacturer of Seroquel, under the supervision of the UM-AHC. This trial targeted participants with homicidal risk and no history of suicidal risk. The study did not allow participants to change drugs if their double-blinded assignment was not working properly. Patients were also not allowed to take additional anti-psychotic drugs during the course of the trial. The patient was followed up regularly throughout the study by a social

worker and occasionally (3 times in this case) was evaluated by one of the physician-investigators.

Despite the patient's mother's account of attempts to warn the investigators about the patient's lack of progress in the trial, the patient remained in the study. From perspective of the mother, the worsening condition of the patient was overlooked by the investigators, thus making the attempts to remove the patient from the trial unsuccessful. Approximately 4.5 months after starting the trial, the patient committed suicide and was found dead in his residence.

When the results of the trial were published, Seroquel was shown to be comparatively effective to Risperdal and Zyprexa. The study noted that two suicides occurred during the course of the trial, and both of the patients were on Seroquel. They stated that these cases were closely followed by their investigators during the course of the study. When the study was shown to other experts in the field, initial concern was shown for the statistical significance of the results. The study measured the effectiveness of the study by the lack of discontinuation of the study. All patients who finished their course of the drug were shown to have effective treatment, despite their condition and its change (or lack of change) during the trial. Experts also think that the study lacks dimension by not including the classic anti-psychotic drugs. Most importantly, concern stems from the thought that the study appears to be market-driven instead of focusing on the advancement of medicine and science.

The case presentation raises a number of ethical concerns, to which I now turn.

1. Capacity to Consent

i. Concern

As stated in the article, when this case was brought to the attention of legal authorities, it was stated that consent was appropriately given because all participants were of similar mental statuses and gave consent (Elliott, 2010). This is particularly troubling because state statute governs that patients who are psychotic and dangerous are incapable of making decisions about their health for at least 14 days after onset of the condition. Since the subject in this case was admitted for treatment under this guideline, he displayed a need for intervention and has the potential for continued states of psychosis beyond the period of institutionalization based on his medical history. With the ordering of continued treatment, the physicians do express concern for the health of the patient, suggesting that his mental status is still in jeopardy beyond this 14 day mark.

As outlined in the *Declaration of Helsinki*, vigilance must be exercised when enrolling vulnerable groups in human subject research (Article 8) (2008). The presence of an unstable mental status may affect the individual's ability to exercise autonomy. Not only may the individual not understand the trial itself, they may not have the capacity for decision-making regarding their own well-being. This document then states that in the case of mentally incapable, along with incompetent and physically incapable individuals, surrogate consent is to be given (Article 23-24). Although it is recommended for assent of the individual along with the consenting decision of the proxy, the inclusion of a rationally

capable surrogate, who is concerned for the well-being of the individual enrolling in the trial, decreases the opportunity for exploitation.

Informed consent has been seen as the cornerstone of research ethics. Ensuring consent is a prerequisite for the ethical conduct of a trial. The execution of consent in this case is especially concerning because the decision made by the subject affected whether he was placed in inpatient medical therapy or enrolled in an outpatient clinical trial. Each of these two choices was described as therapeutic options, which can create a therapeutic misconception when reviewing the clinical trial. In combination with the mental instability of the participant, this decision has potential to not be evaluated reasonably (Shamoo & Irving, 1993). The inclusion of a surrogate in this process could have been beneficial in determining whether to continue medical treatment or to enroll in the trial.

As the trial continued, the mother noted changes in the behavior of the subject and attempted to reach out to the investigators. Based on her impression of her son, she described a decrease in mental capacity, similar to that of his initial admission to the hospital, and thought that trial was not therapeutically beneficial anymore. The investigators rejected her requests for the discontinuation of the trial. The change in mental status could have affected the subject's awareness of his condition and incapable of determining whether to discontinue participation. This is similar to the initial decision to administer medical care because his condition was not stable enough to make proper decisions regarding his health and overall well-being. By not recognizing a shift in the participant's condition, the study and subject is put at risk in relation to the state of autonomy. Each

subject will not express the same mental condition and the uniform protocol should not be used overshadow discrepancy in respect toward the subjects.

ii. Physician Insight

Physician-patient relationships are highly influential in patient care. Although the physician plays an important role in treatment, the patient is also responsible for open communication and autonomous decision making. It is the physician's duty to create a space for the patient to actively participate in this manner. With the establishment of the patient's rationality and intentions of treatment, the physician could be to realize if the patient capacity to act in this role changes or diminishes in any way. Decreased mental capacity should be seen as a danger to decision-making and medical treatment. The autonomy of the patient as well as the health status of the patient is compromised. At this point, the welfare of the patient should be put first and treatment should be reevaluated.

The case of the drug trial shows a decline in mental capacity but no change in the patient's decision making responsibilities. The patient continues to give their status and thoughts of the treatment course to the investigators, via the social worker. At this point, the patient may not be able to engage in the physician-patient relationship as previously done and may not be able to ask proper questions or state concerns about the treatment which would affect the course of treatment. In terms of patients with inability to make competent decisions, a legal proxy is to act on their behalf in the physician-patient relationship. This is highlighted by the AMA for instances of clinical research,

noting increased vulnerability with participation. The physician is to engage with the proxy so that they can make a decision on behalf of the patient. In this case, the mother of the participant (or another proxy) could have discussed the continuation of the trial with the physician and determined an appropriate course of treatment from that point forward. The trial may have been still chosen as that method of treatment, but the vulnerable mental state of the patient would have been better served.

2. Research as Medical Treatment - Coercion and Misconception

i. Concern

Upon enrollment in the trial, the patient/participant was presented with two options. These options consisted of continuing in-patient medical care or participating in the drug trial with out-patient follow up. Medical practice and the conduct of research have distinct goals. Medical practice involves the actions with therapeutic intent and expectation for success whereas research has the goal of advancing current knowledge of the field (*The Belmont Report*, 1991). The knowledge gathered from clinic trials can lead to successful therapy, however it is not the immediate goal or expectation of participation in the trial. Although these two choices can be ethically sound standing alone, trouble can arise when pinning them against each other. It creates the perception that each option has equivalent therapeutic benefit, a misconception that should be controlled in order for proper consent to be given. This can be seen as coercion for enrollment and is not ethically justifiable.

The terms of enrollment can also be seen as a potential for coercion. The settings of the two options differed greatly. Medical treatment would cause the participant to be essentially institutionalized, where the trial allowed the patient to continue living out of the hospital, in a half-way house. The perks of a more independent atmosphere can be seen as a draw toward the option of enrollment. In combination with the participants' uncertain mental status, these differences can be magnified and unjustifiably influence the participants' decision to enroll.

Also, medical practice and research fall under two distinct bodies of legislation. In medical practice, the physician engages in a contractual relationship with their patient. The physician acts to increase the well-being of the patient based on their medical complaint at the formation of the relationship. Harm caused from improper informed consent to deviating from the standard of care can be grounds for neglect, a legal responsibility of the physician. This reflects the goal of medicine to take actions to increase the health of the individual. The physician is responsible for using medical knowledge and therapy diligently to promote therapeutic outcomes.

Research, on the other hand, is regulated differently. When consenting to research, foreseeable harms are accepted as a part of participation. It is up to the participant, and sometimes the investigator, to decide whether or not to stay enrolled in the trial based on changes in well-being. The investigator may even provide a set compensation or medical care in some cases of harm, but it is not a requirement. Overall, the investigator is not held personally responsible for health outcomes of the participant, even if he/she is also a physician. Without

understanding the differences in between practice and research, the participant may not understand the responsibility of the CI in cases of harm or unsuccessful attempts at therapy. This could affect their decision on whether to choose the clinical trial over the medical treatment, or vice versa.

ii. Physician Insight

It is stated in the AMA's Code of Ethics that physicians participating in research are not to act in ways that may coerce the participant to enroll in clinical trials, including through exaggeration of the benefits or any false understanding of the purpose of the trial. By acting in this way, the welfare of the patient can be compromised, which goes against the principles of medical practice and decreases trust within the physician-patient relationship. Clinical research as treatment is not unethical in itself, but it requires physicians to manage additional conflicts of interest and potential for misconceptions by the patient.

Physicians are required to provide patients with options for treatment on a daily basis. They present the risks and benefits of different therapies and can guide the patient to the making a choice on their treatment plan. Maintaining autonomy during this process is crucial to protecting the well-being of the patient. Adding the option of a clinical trial for treatment creates another layer of complexity in avoiding undue influence on their decision. The AMA suggested that informed consent for the trial should be done apart from the physician-patient relationship, so the goals of research have a lower chance to get misconstrued. But, as stated by the APA, it is the provider's duty to maintain fidelity and

responsibility in managing any conflicts of interest, like those arising from the duality of medicine and research.

Beyond the complexity of presenting research as a treatment option, physicians must maintain that they are treating a human during the course of treatment, not the disease, as set out in the Hippocratic Oath. Similarly, the patient is an individual, not the product of research subject qualifications. The discussion and recommendation of treatment options, including research, should reflect the needs of the individual and their well-being, not the interests of the research trial's need for participation. In this case, the terms of the treatment options may have swayed the patient's decision. Especially knowing the fragility of the patient's mental status, physicians may have approached the decision making process differently in order to improve the patient's ability to make an autonomous and health-focused choice.

3. Research as Medical Treatment - Quality of Care

i. Concern

Continuing with the blurred perception of research and treatment, the consent in deciding between in-patient medical care and out-patient trial participation should clearly distinguish differences in medical follow up. The mother of the subject reports that follow up was rarely completed by a physician or psychologist. Instead, the participant was visited by a social worker. Although the social worker can discuss with the patient and conduct any survey provided by the trial, they do not provide the same kind of care as a physician, psychiatrist or

psychologist. With these visits occurring with days in between, quick changes in mental status may not be recognized at their onset and result in harms that could have been avoidable.

This choice of follow up in itself is not ethically unjustifiable, but when the trial is placed as an option against the in-patient medical care, discrepancy in quality of follow up is assumed to be sizable. Stemming from the use of this research trial as a treatment option, the follow up by the social worker greatly differs from the monitoring of in-patient medical care. Although the amount of time given in the follow up may be the same in each location, the accessibility to care upon changes in mental status is significantly greater when in the hospital. Also, the administration of the drug is monitored by medical personnel when in the hospital. The understanding of these differences may make a difference when determining whether or not to participate in the trial. Overall, the expectation of medical follow up for the option chosen should be recognized and understood, which may have been blurred in this example with non-institutionalization being offered to the patient.

Although it is not a requirement of investigators in research, the fact that the participant was not removed from the trial when therapeutic benefit was not achieved, actually showing a decline in mental status, is unsettling. In the subject's initial 14-day medical hold, the patient was placed on a drug regimen of Risperdal and did not show a similar decline. In fact, after the course of the drug, the subject was deemed as capable to make rational decisions regarding his

health, an improvement from his initial state of incapacity. This choice of treatment was seen as successful in this time frame.

Risperdal was one of the drugs under comparison, but the blind nature of the study hid the identity of the drug given to the subject. Therefore, the subject had potential to continue with the course of the medical, which had proven beneficial to the point of enrollment. However, the patient was placed on another drug, Seroquel, and did not have a favorable response. With the decline in the health of the subject, it is concerning that the investigator did not discontinue the course of the experimental drug (also unknown to the investigator) and restart the course of Risperdal. The harm caused to the subjects was foreseeable and avoidable, but the study continued. Although the drugs used in the modern case are FDA-approved, it cannot be expected that they will work effectively for each patient. And, if a standard of therapy exists for that patient, it should be implemented in the case of health decline when using a blind drug trial.

Although this should apply in cases of varying severities of health conditions, the ramifications of symptom onset in this case creates harm for both the patient as well as others around them. The subjects that were enrolled in the study presented with homicidal ideation, meaning they stated plans of killing others when experiencing a change in mental status. When showing a decline in mental status, the subject should have been removed from the trial, decreasing the potential for harm in this manner. This decline did lead to the suicide of the subject, an outcome that may have been avoided when a known successful therapy existed.

ii. Physician Insight

Physicians not only have an obligation to give respect and dignity to the patient, but to be responsive and provide care in a timely manner based on the physician patient relationship, as described by the AMA. In this case, the arrangement for follow up by the Social Worker may have caused miscommunication in the care regimen for multiple reasons. Despite the cause of this gap in information, the patient was not cared for in a responsive way or a timely manner. It can be inferred that the lack of response to the patient's decline is what led to the outcome seen in the case. Therefore, with insight of a physician along with proper communication between those involved in the administration of the trial, the failure of the experimental drug could have been recognized earlier and a return to the initial treatment could have improved health outcomes.

If the researchers had used the ethical standards of clinical care rather than research, individual outcomes might have been significantly improved. As stated in the Hippocratic Oath, physicians are to prescribe treatment regimens to the best of their skill and to not cause harm to the patient. The physicians involved in the case had the known ability to treat the participant's condition and not cause harm, as seen in the holding period prior to the decision to starting the trial, but did not act on this knowledge when the trial drug did not improve the health status of the patient. The physician is to practice medicine to the best of their knowledge and judgment, which may have led to a change in treatment - the removal from the

trial. As stated in the AMA's Code of Ethics, it is principle that physicians should put the welfare of patients first. The patient's health comes before expectations of institutions, personal endeavors, and clinical research itself. And, above all, the patient's well-being trumps progress of the clinical trial. In this case, the patient's welfare appeared to be compromised from the decline of the patient's health during the drug trial. The role of the physician would address this concern before handling the remainder of the trial or any personal dedication to the project. By focusing on the health of the patient, the potential for harm may have decreased.

Chapter 4

ARGUMENTS

1. Tilting Scales: Ethos & Regula

As seen in the history of clinical research, legal regulation of research has taken on a role of translating clinical research ethics standards into governance of the execution of drug trials. The effectiveness and weight of current regulation in human subject research must be reconsidered. The structure of the trial in the case study presented with, what appears to be, great odds for success in the balance of the protection of human subjects and quality scientific results. This research was being completed at a well-known research institution within the academic setting. The academic setting provides access to experts in the field, education of both medicine and science, resources necessary for the completion of research, a well-developed health system, and the protection of a regulated institutional review board, to name a few. But, despite the abundance and quality of these resources, the current regulatory format still failed to illuminate problems in the research endeavor that compromised the beneficence, the respect for subjects, and justice of the trial.

The case presented here seems to fall into the same trend seen in the history of research regulation. People are harmed when participating in a research trial, resulting in a negative public response to clinical research. This was seen in the cases of the Nazi War Crimes, the cases discussed in Beecher's publication, and the Tuskegee Syphilis Trials. Historically, the next step in cases of this nature

was the ordering of reform to the regulation. So, if this trend would continue, the flaws seen in this modern drug trial would catalyze the addition of more legal requirements on research to account for the new challenges presented. But, more than anything, this trend should demonstrate that regulation is not successful and lagging behind many issues in modern clinical research. If flaws in research are happening within this high tier of scientific research and they are not revealed until the investigation of the death of a participant occurs, it calls into question what other lapses in participant protection are overlooked within the current regulatory structure of clinical research.

With the failure of regula to providing sufficient protection of human research subjects, a shift back toward the prominence of ethos in research and practice may be the next best option. However, it is difficult to imagine completely reverting to the structure of ethos with the dramatic changes regulation has played in the structure of clinical research. Problems seen in the execution of medical research governed by ethos catalyzed both national and international regulation. The protection of human subjects in research was not shown to be successful under the discretion of physicians and scientific investigators alone. Especially with challenges of conflict of interest present among pharmaceutical research today, placing trust in the individual to manage this tension without bias could get messy and cause even more exploitation of participants.

A strategic balance among ethos and regula must be achieved in order to best protect participants of clinical research. The strengths and intentions of each

have shown to weaken in instances where one took precedence over the other. Although law and ethics have the ability to contradict, the use and practice of both ethos and regula is dependent on the other. The success of this relationship is contingent on correct perceptions of both regulation and ethics standards by the CI in correlation to the execution of research. This case's concerns and analysis illuminate relevant misunderstandings of regula and ethos, which can negatively affect participant protection. Understanding these misconceptions can provide insight to the future development of regulation and ethical standard as well as the practice of medicine and clinical research.

2. Misconceptions of Regula - IRB Approval

The IRB is in charge of accepting or denying a research trial for continuation with the use of human subjects. This process includes portions that focus on the protection of subjects, including statements of participation selection, informed consent, and expected risks and benefits of the trial. Once approved, the trial is able to proceed with the accepted protocol. In a recent survey by Fisher, physicians had the understanding that the trial was ethically sound when becoming a CI for an approved trial (2008). This shows that a blind trust may exist in the current regulatory system of clinical research to determine what is considered ethically-justified. The reliance on the IRB in this way could be contributing to the questionable treatment of research participants.

Safeguards placed throughout the protocol application can be designed to help to control compromising scenarios, but this may not translate properly when

the trial is active. The investigator should be able to identify the ethical issues of the trial and take action to protect each individual subject. This is especially important when executing informed consent. Although the proper information about the trial and the documentation has been approved by the IRB, not all participants may be able to comprehend the information at the same level. The aforementioned trial acts as a relevant example of this due to the variation in mental statuses of the participants involved. Each participant could require individualized attention to best ensure the protection of their autonomy as well as throughout the course of the protocol, which is a responsibility of the investigator.

As described by Fisher, some physicians executing research protocols believed that the management of ethics was not a personal responsibility since the trial had been approved by an institutional review board (2008). The fact that the IRB proposal for the trial addresses the ethical challenges presented it in the case and is approved does not relinquish the responsibility to monitor for these challenges during the course of the subject's participation. Ethics must be addressed continuously while the trial is occurring and is a primary responsibility of the investigator, despite their level of involvement in the trial development. CI's should expect to take an active role in the 'practice' of clinical research ethics instead of relying on regula to ensure participant protection. Overall, the skewed perception of regula in human subject research may be unintentionally restraining investigators from accountability for the protection of subjects during the trial.

3. Misconceptions of Ethos – Clinician Investigators and Duality

The conflict of the duties of the physician and scientific investigator within the role of a Clinician Investigator tends to cloud the discussion of CI research ethics. Specifically, the balance of these two sets of ethos has yet to be achieved. This is concerning seeing that both physicians and researchers have sound standards of ethics that are widely accepted. Currently, ethical standards have suggested that physicians work to separate their designation as a medical provider to avoid misconception on the part of the research subject. Although it makes sense for the physician distinguish the goals of research from therapy when acting as a CI, having the physician assume the ethos of the scientific investigator and abandon physician ethos may not present the best opportunity for patient protection. The misconception of ethos within the ‘resolutions’ of this duality can pose a hurdle to participant protection.

Patient welfare stands at the forefront of both medical practice goals and ethos for the physician. Though the purpose of research may be to promote the advancement of scientific knowledge, an aspect to research ethics is protecting the welfare of the participant, although not therapeutic in nature. In this similarity, the rise of the Clinician Investigator may shift from a challenge to an advantage in the personal development and execution of ethos. With practice in medicine grounded in values encompassing patient protection and personal responsibility in the physician-patient relationship, participants may be more suitable hands of an investigator with the ethical experience of a physician.

Using the patient care experience of the physician during research does not necessarily lead to the goals and protocol of the trial being compromised. Research will continue to serve the purpose to increase the knowledge of the field, not to provide medical therapy. The physician's relationship with the patient does not suggest they will promote treatment over research, but that they will be able to identify the best suited participants for the trial. The institutions and companies involved in the development of drugs and medical devices will still stand at the forefront of the creation of protocols and their execution. Trials will follow protocol, with exceptions being for declines in health. Removal of subjects with declining health should not compromise the trials, for the serious side effects will demonstrate ineffectiveness of the drug as well as a fatality. It could even help the research institutions and companies avoid legal action resulting from cases of avoidable harm. Any change to increase the follow up of patients will only provide the trial with more data. Also, the participation of the physicians could help to disperse any information gathered in the trial to the health environments which they already exist.

The experience of physicians could enhance the informed consent process in creating an open environment for questions and discussion. The familiarity of relationships with physicians could enhance the initial trust in the trial. The participant may be more comfortable to ask questions in order to come to an autonomous decision. The physician's knowledge of health could provide additional questions participants have about the risks and benefits of the trial.

Medical experience could give participants an additional sense of security in the case that side effects do occur and medical attention is needed.

The patient's well-being throughout the course of the trial can also be enhanced by the physician's ethos in clinical research. The qualities of responsiveness and timeliness of care will improve the protection of patient's in cases of harm and declining health. The participants in need of additional care outside of the trial will be recognized and transfer of care will be addressed. The continued focus on the participants will help to manage any conflicts of interest, including obligations to the institutions and personal goals. Treating participants with the care of patients will help to promote their well-being throughout the research process and improve participant protection. Although it may appear to solve problems in therapeutic misconception by creating a division between the roles of research investigator and physician, abandoning patient-centered values to execute trial protocol may compromise the welfare of subject. The CI may be able to better protect subjects through maintaining their values from medical practice while acting as research investigator.

Chapter 5

CONCLUSION

As seen in the reviewed case study, even the most potentially strong foundations for ethically standardized and closely regulated research are quaking at the onset of new challenge in contemporary research trends. More scrutiny must be made of both the legal regulation and ethical governance of clinical research as for-profit pharmaceutical research moves beyond the academic setting and into private practice, away from the applauded oversight of academic institutions.

Through better understanding the purpose of regulation and ethical standard in relation to the personal responsibilities of the CI, increased subject protection can be present in the development, approval and execution of clinical trials. Misconceptions of both the regulation of clinical research and the moral norms of physicians and researchers will continuously need to be managed in order to promote personal responsibility of the CI to be involved in the ethics of the trial. But, through bridging the discrepancies in both regulation and ethics, movement can be made toward protecting the well-being of subjects while leaving room for scientific innovation to continue in both the academic and private sector settings.

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