CHAPTER 4

Evolution of Regulations

Students working in basic research may someday see their discovery ready for clinical application. A former student contacted me to ask about post-graduate training in regulatory compliance in order to see her discovery to the market and bedside. Students working in the pharmaceutical industry or in clinical settings may have a greater understanding of the process of approval required for a new drug. All graduate students should have an understanding of the requirements. Discovery of viral inhibitors, new anticancer drugs, vaccines, or other treatment strategies progress from basic research, through animal model testing if possible, and then to clinical trials with human subjects. The data from the clinical trial is used by Food and Drug Administration (FDA) to determine if a new therapeutic is safe and efficacious enough to be released to the market. The ethical standards for research with human subjects have evolved through the work of conventions, such as the Nuremburg Code, and into the Code of Federal Regulations (CFR), often called the Common Rule.

Evolution of ethical codes for research with human subjects

Nuremberg Code (1947)

Declaration of Helsinki (1964)

National Research Act (1974)

Belmont Report (1978)

4.1 NUREMBERG CODE

The Nuremberg Code listed ten articles about human subjects' experimentation. It was a response to the American military tribunal criminal proceedings against leading German physicians who participated in medical experiments on thousands of concentration camp prisoners without their consent. Andrew Ivy and Leo Alexander working with the prosecution team submitted a memorandum for the "Permissible Medical Experiments" with ten points that would be called the Nuremberg Code (Ivy, 1948). The first point was "the voluntary consent of the human subject is absolutely essential" including "sufficient knowledge and comprehension" by subjects "to make an understanding and enlightened decision."

The Nuremberg Code, (1949)

Introduction: "In 1945, the Allied nations (U.S., French Republic, United Kingdom, and Union of Soviet Socialist Republics) established an International Military Tribunal for the prosecution of German citizens accused of war crimes and crimes against humanity. At the end of the following year, an eight-month trial of twenty-three Nazi officials, twenty of them medical doctors, began. These defendants were accused of crimes against humanity by conducting criminal scientific and medical experiments on concentration camp prisoners. The "Doctors Trial" concluded on August 20, 1947, with a verdict of guilty imposed on sixteen defendants, of whom seven were sentenced to death. The final judgment concludes with a statement of ten points enumerating the principles for ethical research with human subjects. These ten points, subsequently known as the Nuremberg Code, have become part of International Law and serve as the basis for many formulations of the ethics of research with human subjects."

The Nuremberg Code never became international law but it laid the groundwork for the expectation of informed consent as a process and a document. Informed consent was adopted in Article 7 of the United Nations International Covenant on Civil and Political Rights (1966) and in the International Ethical Guidelines for Biomedical Research Involving Human Subjects sponsored by the World Health Organization and the Council for International Organizations of Medical Sciences (1993) (Shuster, 1997).

In 1953, the Clinical Center of the National Institutes of Health opened and welcomed "volunteers" who were not in the clinical sense, patients. Investigators did not immediately see that the relationship between a physician and patient is different than the relationship between a research subject and research investigator, who may also be a physician. In an NIH-sponsored survey of its grantee institutions in 1962, only 9 of 52 departments of medicine had policies regarding research with human subjects (Jonsen, 1998).

4.2 HELSINKI DECLARATION

The Helsinki Declaration adopted by the World Medical Association in 1964, reiterated the need for voluntary informed consent, and placed emphasis on risk-benefit ratio in design of the research study. The Declaration applies to international research ethics. Research is defined as either non-therapeutic or research combined with clinical care. The Declaration reinforces the Nuremberg principles of informed consent and the expectation that before using human subjects the therapeutic agent will be tested in an animal model wherever possible. It adds a requirement for review by an independent ethics committee.

Leaving these responsibilities to the investigator was inadequate as shown by Henry Beecher's (1966) article "Ethics and Clinical Research" published in the *New England Journal of Medicine* in 1966 highlighted 22 studies which presented ethical questions about the conduct of clinical research. The cases selected came from the published literature. Some examples of "unethical or questionable ethical studies" included research conducted on patients without informed consent, research studies for which there was no expectation of direct benefit. The consequence was increased vigilance for independent ethical committee reviews prior to beginning enrollment of human subjects in all clinical trials.

Through seven revisions to date, the latest in 2013, the World Medical Association's Declaration of Helsinki has been an international guideline for ethical principles applied to research with human participants. The first revision of 1975 added the requirement for research ethics committee review. Interestingly the U.S. adopted Institutional Review Boards (IRB) whereas other countries adopted the term, Research Ethics Committees (REC) or some variation of it (World Medical Association Declaration of Helsinki, 1964).

4.3 COMMON RULE

NIH issued policies for the Protection of Human Subjects in 1966. In 1974 the U.S. Congress passed the National Research Act establishing a Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Public Law 93-348). The Regulatory framework in the U.S. is codified in the Department of Health and Human Services (DHHS) regulation Title 45 Part 46 Code of Federal Regulations (CFR) with specific parts dedicated to vulnerable subjects, and a separate set of regulations for investigational drugs and devices under the oversight of Food and Drug Administration (FDA). The FDA regulations are codified in Title 21 Parts 50 and 56 of the CFR. Specifically, researchers must obtain approval before conducting research involving human subjects as described in the Common Rule (Federal Policy for the Protection of human Subjects (Common Rule) @ www.hhs.gov/ohrp/humansubjects/commonrule).

45 CFR 46.102: Protection of Human Subjects: Definitions

"Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities."

Human subject means a living individual about whom a investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual or

(2) identifiable private information"

(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html)

4.4 BELMONT REPORT

The "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research" is the product of the National Commission (Public Law 93-348) to guide independent ethics committees in the ethical analysis and resolution of ethical problems arising in Research with Human Subjects. "On July 12, 1974, the National Research Act (Pub.L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles" (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm). The report focuses on three principles: Respect for Persons, Beneficence, and Justice. These are not intended to exhaust all possible ethical considerations when reviewing a research proposal, but to guide the deliberations of the IRB (Steneck, 2007, pp. 37-43).

CHAPTER 5

Belmont Principles

Respect for persons stresses the autonomy of the subject, as one free to decide on the basis of understandable information whether to voluntarily enroll in an experiment as a participant. The same principle recognizes that some individuals may lack the cognitive maturity and ability to reach willful informed choices and therefore are entitled to additional protection. The practical application of respect for persons is informed consent, the process through which research investigators inform potential subjects about the study, its risks and benefits, conditions used to protect privacy and confidentiality, alternatives to participation in terms of treatment or care. In short, everything a rational person needs to know in making a reasoned choice about participation.

Beneficence as a principle means to help including the duty to minimize harms. In human subject's research, beneficence invites an analysis of risks and benefits in the study being proposed. Research is an activity designed to test a hypothesis, permit conclusions, and develop generalizable knowledge. Therefore the benefit may be for future patients, not those in the study. Under such conditions, minimizing harm in order to produce future benefit is crucial.

Justice requires fair and equitable treatment among persons, in human subject's terms it applies to equable or fair access to the study. In this context justice is distributive, involving how benefits and burdens are shared among a similar group of persons. How fair sharing of benefits and burdens is understood in a given context can be controversial. The Commission intended that selection of subjects not be restricted to one socioeconomic group or from persons not likely to benefit from the results (Levine, 1986).

Case 9: When Does Research Begin? (Murphy 2004, p. 31).

In 1995, John Wilmoth met Christian Mortensen at a retirement home. Wilmoth, who was a demographer at the University of California at Berkeley, had heard Mortensen was 112 years old. Wilmoth believed that it would be interesting to confirm this man's age, because he would be among the world's oldest men. He thought he might conduct interviews to add a human-interest angle to articles he would write on human longevity.

Wilmoth consulted Mortensen's legal guardian and his doctor, who agreed that such contact would be good for the older man's social stimulation. At the first meeting, Wilmoth asked Mortensen questions such as "Gee, how old are you? When were you born? What brings happiness to your life?" The two continued to chat frequently over a few months. Then Wilmoth

contacted his university's IRB because he wanted to give Mortensen some mental agility tests. On learning of the meetings with Mortensen, the IRB accused Wilmoth of failing to report contact with a vulnerable human subject, and in 1996 the university began a misconduct investigation. Wilmoth saw himself as a victim of "regulatory mania." In 1998, Mr. Mortensen died at 115 years of age.

Discussion Questions

In what way, if any, did Professor Wilmoth's conversations put Mr. Mortensen at risk? Was there any benefit from the conversations?

Do you think Wilmoth should have sought review and approval for his initial conversations with Mortensen?

The misconduct investigations concluded Wilmoth did nothing wrong. How could the institution have avoided such an investigation?

5.1 INSTITUTIONAL REVIEW BOARD (IRB)

The IRB functions at the institutional level and is required for all research sponsored by federal funds, and DHHS requires a written assurance that all research is conducted according to federal regulations. IRB membership should include a scientist, a nonscientist, someone unaffiliated with the institution, and the range of expertise necessary to review the scientific study and apply the Belmont principles and abide by the Common Rule. IRB review should address whether the informed consent process is accurate and understandable, if the research design is most likely to yield generalizable knowledge, investigator competence, compensation for research related injury is not coercive and that adequate provisions are made to ensure privacy and confidentiality of subject personal information. The basic normative value is honesty. The IRB members trust that the investigator will follow the approved protocol, report adverse events, petition for administrative changes, and provide annual updates on ongoing research. The commitment of time is significant for IRB members. Conversations are ongoing about how to streamline the approval process without compromising the merit of ethical consultation (Levine, 1986).

Millum and Menikoff (2010) call for more attention to legitimate use of expedited review, exemptions and centralized review to curtail some of the IRB volume. It may be that IRBs are overly cautious because of the threat of retributive enforcement of federal regulations. Careful attention to exempted research such as surveys, mining existing data so long as personal identifiers are masked, can reduce the number of protocols being reviewed. However, even when these factors are considered, the workload and dependence on volunteer service on the IRB can be burdensome.

Students should imagine that they will at some point in their career serve on an IRB. Likewise students should know what the IRB responsibilities are when research they are submitting is reviewed.

5.2 CASES TO HIGHLIGHT BELMONT PRINCIPLES

Cases 10-12 are selected to highlight the three Belmont principles, and helps us see where the ethical principles align with the pragmatics of the research. While each case is not restricted to one principle, one of them is primary (Veatch et al., 2010).

Case 10: "Chemotherapy Risks: Is Going without Chemotherapy a Benefit? (Veatch et al., 2010, pp. 343–344)

"Laurie DeSoto, a 16-year-old girl who had recently been diagnosed with leukemia, came to the Pediatric Oncology Clinic with her mother to discuss treatment options with Dr. Elizabeth Holmes, the oncologist who had assumed responsibility for her care when she was referred to the clinic. Several different chemotherapy regimens were under consideration, but Dr. Holmes thought Laurie might be an ideal candidate for a research protocol now under way at the clinic.

The protocol involved a standard four-drug-regimen that had been used successfully for Laurie's type of leukemia for several years. The original regimen required patients to be on the drugs for five years. After considerable experience with this drug schedule, oncologists began to suspect that the patients on it did not need to continue the drug for five years. The data from long experience showed that three years was just as effective as judged by the percentage of patients who remained leukemia free for five years. The three-year regimen was now the standard. It was used widely in oncology programs throughout the United States and elsewhere.

On the basis of that experience, Dr. Holmes and several colleagues began to wonder whether two years on the regimen might be as effective. They realized that the adolescents taking the drug had to endure the side effects of the chemotherapy, the nausea, hair loss, and other effects, and would appreciate having to stay on the regimen only two years rather than three. On the other hand, if they were wrong, it would mean that some patients taken off the regimen after the shorter period might have recurrence of their disease – a terrible, potentially fatal result.

Dr. Holmes had become the principal investigator of a new research protocol that would randomize patients to receiving either the now-standard three-year regimen or to an experimental group that received exactly the same drug combination, but received it for only

two years. It included preliminary evidence from several clinical cases in which, for various reasons, patients had stopped the treatment after two years and had not had recurrence of their leukemia. The protocol had to be approved by the hospital IRB, the group charged with protecting human subjects of research. One of the criteria for approval was that the risks to subjects were reasonable and were justified by the potential benefits. The review board, after considerable discussion, voted, by a eight to two margin, that the risks were reasonably balanced. In other words, the majority of the board thought that the small risk of greater chance of recurrence of the leukemia was justified by the benefits to the youngsters who received the shorter two-year regimen.

Dr. Holmes now decided to present the opportunity to enter this protocol to Laurie DeSoto and her mother. If they agreed to enter the study, Laurie would be assigned randomly to either a standard three-year regimen or an experimental two-year treatment. Although subjects of research are normally "blinded", that is, kept ignorant of which treatment arm they enter, in this case, that would not be possible since patients and physicians would clearly know whether they were receiving the treatment for three years or two. If the investigators and the IRB believe that the risks and benefits are more or less equally balanced between the two groups, such randomization is considered morally acceptable. When two treatment arms in a research protocol are perceived as being equally balanced in their risks and benefits, the study is said to be in equipoise. Since Dr. Holmes and the IRB agreed that the risks were evenly balanced, they considered the offer to be randomized morally justified.

Dr. Holmes presented the study to Laurie and her mother including the fact that, if they agreed to enter the study, they would be randomly assigned to either three years or two years of treatment. After being given an opportunity to ask any questions, Mrs. DeSoto signed the consent form on behalf of Laurie. Laurie, as a minor, could not give her own consent, but was nevertheless asked to give her assent, which she gave. This amounts to approval even though it is not based on the level of understanding and voluntariness that we would expect from an adult.

Dr. Holmes, having received documented consent, left the room and soon returned with the news that Laurie had been randomly assigned to the three-year arm, that is, the existing standard treatment. To her surprise, Laurie burst into tears. When asked, she explained she really wanted the two-year treatment course. She hated the thought of the side effects, especially the hair loss. She did not want to look strange for any longer than necessary. She sobbed in her mother's arms as Dr. Holmes looked on. Had Dr. Holmes and the IRB assessed the risks and benefits properly?"

Discussion Questions

Specifically identify what the risks and benefits are in this case. Do you consider the risk (leukemia recurrence) and the benefit (less adverse effects of chemotherapy) objectively or subjectively?

Since the IRB's duty is to consider risks and benefits along with other important aspects, such as the consent process, and fair access to the trail, confidentiality, design and so forth; is the primary issue risk and benefit? How is the risk benefit assessment by Laurie different from that of the IRB?

What could be done to better inform Laurie and her mother, or were they adequately informed? Can you construct an alternative way to present choices to Laurie and her mother?

What would examination of respect for persons—autonomy and informed consent—reveal in this study?

The primary risk is recurrence of leukemia from the perspective of the reviewers and professionals conducting the study. Laurie appears to think extended time on chemotherapy with the accompanying side effects the primary risk. Would a conversation about what is a risk and benefit help? Was it clear to Laurie that the benefit of three years of the treatment had a known high probability of keeping the leukemia from recurring? What role, if any, should emotions have in risk-benefit assessment? Does the family think the doctor is objectively presenting the options or is there an assumption that only what is best for the patient is being offered? Is the distinction between the therapeutic relationship of doctor and patient in contrast with researcher and subject clear? (Veatch et al., 2010).

According to the Belmont Report, respect for persons means free informed choice, exercise of self-determination that affirms autonomy. When a subject is under the age of majority (which varies by country), a parent can give proxy/surrogate consent, but when the subject is of an age to understand the research purpose, to evaluate the related risks and benefits, an assent document is used (simplified readable version of informed consent document appropriate to the age of the patient). When or if parent and child differ in their assessment of risks and benefits, whose freewill ought to be considered the appropriate consent? Would more conversation change the perspective of Laurie? Would the mother change her mind after seeing the effect it has on her daughter? Should the physician offer an option such as taking the standard three year dose of chemotherapy, outside of the research study and later making the decision to stop chemotherapy after two years? Is randomization justified in this trial?

The answers to these questions as you discuss them in a group may vary significantly. How do you reach a consensus? What is your underlying ethical rationale? Does the discussion reveal points of consideration that you did not consider on your own? How is the case helpful in understanding the IRB obligation to ensure the best possible risk-benefit ratio?

IRBs have more to consider than risk-benefit and autonomy. The Belmont Report includes justice which directs attention to subject selection. Are particular groups of people more likely to be recruited to a research trial than other groups? Why is this particular group sought for this study? Is recruitment fair in how it reaches out to the community, or the process through which it recruits subjects? In addition, justice means evaluating the design and conduct of the research. If accommodations can be made to increase the equitable enrollment of persons, should the IRB advocate for a change in design?

Case 11: Justice in Research Design: Being Fair to the Critically Ill (Veatch et al., 2010, pp. 355–356)

"Cancer researchers at a major medical center wanted to conduct a pilot study of a five-drug combination using high doses of chemotherapeutic agents. The drugs were cyclophphamide, adriamycin, VP-16-213, vincristine and methotrexate. The first four were drugs long known to researchers. The side effects anticipated included nausea, vomiting, myelosuppression (inhibition of cells to be made in the bone marrow resulting in low numbers of blood cells), stomatitis (inflammation of the mouth and lips), alopecia (hair loss), and cardiomyopathy (damage to heart muscle). The patients to receive these were seriously ill with tumors that were resistant to standard therapies.

The fifth drug, methotrexate, also posed the risk of side effects including myelosuppression, stomatitis, occasional hepatitis (liver damage), nephrotoxicity (kidney damage), and neurotoxicity (nerve damage). These were of particular concern when the drug was given in high doses. The proposed study would administer 1.0 g/m2, a relatively high dose. The toxic effects would be neutralized by administering leucovorin intravenously 24 hours later followed by three days of oral administration. This strategy would permit administering higher doses of the methotrexate. It was referred to as "methotrexate with leucovorin rescue." The protocol called for administering the drugs on a 21-day cycle with methotrexate given on the fifteenth day. All drugs were to be administered on an outpatient basis, except that the methotrexate and intravenous leucovorin would be administered on an inpatient basis, thus keeping the patients in the hospital for 24 hours out of every three weeks.

The IRB reviewed the protocol focusing first on the traditional questions of the risks and benefits of the five drugs. The debate soon focused on the methotrexate and leucovorin. Some

IRB members were concerned that the oral leucovorin would be given to the patients to take at home. Given the severity of the patient's illness and the general propensity of patients to miss doses of medication, the IRB members were concerned that some patients might forget their rescue medication, which would result in death. It was noted that a patient could even intentionally omit the oral leucovorin in leaving an exposure to a potential lethal result. It would amount to suicide by drug refusal. These IRB members proposed that it would be safer for patients to remain in the hospital for the three days to assure they received their leucovorin in rescue appropriately.

A second contingent of the IRB membership expressed a different concern, one shared by the investigators. They feared that requiring patients to remain in the hospital for 3 days out of every 21 would tax the resources of the research ward of the hospital. Other research projects might have to be put on hold while the research beds were devoted to this use. Concern was expressed not only about the costs, but also about the burden on personnel. They also pointed out that the goal of the research was to develop a regimen that could be used widely. Administration of the oral leucovorin at home was a more plausible strategy considering the overall costs and benefits.

A third group of the IRB focused not on the protection of patients or the impact on the institution, but on two other ethical concerns. First, they observed that some patients might find the original protocol with oral leucovorin taken at home too burdensome, while others might find being hospitalized for 3 out of every 21 too much to ask. Since these were critically ill patients who were probably dying, this would mean asking them to spend as much as one-seventh of the rest of their lives in the hospital when they really did not need to be there. This group proposed modifying the protocol to permit patients to choose either inpatient or outpatient administration of the oral leucovorin depending on which method the patients wanted.

The research design purists were unhappy with this proposal. It meant introducing another variable into the study. They preferred that all patients be treated identically. To this the defenders of the patient choice provision introduced another argument thus raising a new moral principle. They observed that in this protocol, the patients who could become subjects were very severely ill with drug-resistant tumors. They were probably going to die soon even with the treatment. Thus they could be said to be among the worst off in society. It raised the question of how much researchers could ask of this especially vulnerable and burdened group. They proposed that the modification of the protocol was particularly called for in this case because the potential subjects were among the worst off patients, and they had a special claim of justice to be burdened as little as possible by the research. Since they were the only

patients who had the cancers that were appropriate for this risky research, it was appropriate to ask them to be subjects, but in designing the research, the patients had a right to expect that the protocol would be attractive to them as possible.

This, they claimed, required modifying the protocol to give this group of patients the choice of where they should receive the oral leucovorin even if it meant that the costs were going to be greater than the original outpatient design and even if the research design was not as clean as it would have been with all patients receiving exactly the same treatment.

The IRB faced the choice: should patient medical benefits be maximized by requiring all to receive the leucovorin in the hospital, should total social benefit be used to justify the original home-based administration, or should respect for patient autonomy and justice require permitting this group of patients to choose, even though the costs would be greater than exclusive home based administration and the research design would be slightly inferior" (Veatch et al., 2010, pp. 355-356).

Discussion Questions

In this case do you align with one of the three subsets of IRB members?

Is one concern greater than another?

Is compliance a reason to either change the protocol to achieve assurance that doses are taken, or to exclude a participant?

What might noncompliance do to the data if one or more of the subjects did not adhere to the protocol?

Is noncompliance equivalent to suicide?

What if the patient asks what the doctor would recommend? Does this affect their autonomy? Would the doctor make a recommendation?

The focus on medical benefit for the patients represents the concern of one group of IRB members. The second group wanted to see maximization of benefits at a social level including concern about extra costs to the hospital research unit. When should an IRB be allowed to insist on a change of protocol that also has budget impact on the study? The third group emphasis is on both autonomy and justice. Patients should have the freedom to choose whether the fifth drug is administered at home or in hospital. In this particular study, it is necessary to recruit very sick people because they are the only ones with any potential to benefit. The gravity of their illness highlights their vulner-

ability and therefore IRB members may have the duty to offer extra protection. Is it the case that justice applies at two levels: in recruitment and in design?

Because the consent process seeks to inform subjects sufficiently to permit a voluntary choice, language is important. Terms should be defined and the choice of words should be understandable to the average person. The point of the consent process is to help the subject understand what the study design is, what the potential risks and benefits are, and all information needed to make a choice. If the side effects of a drug are known, it is included either within the consent form or as an information sheet. Putting the side effects in an information sheet risks the perception by subjects that it is less important than the consent document. If the consent document also includes all of the side effects, the risk is that the document becomes too large and complicated for an average person to comprehend.

It is fairly clear that physicians will differ on how much a patient needs to know in order to make an informed choice, reasoning that it may be impossible to convey to the patient all the information available to the professional. To overburden a patient with every possible outcome to a treatment, whether in a clinical study or used in therapy, may confuse rather than clarify information. In the age of the internet, patients are more likely to be more informed about their illness and more inclined to want more disclosure than the physician may think. The "reasonable person standard" aims to disclose what a reasonable person would want to know. The details desired by one reasonable person will differ from another reasonable person, just as the physician's opinions will differ about how much to disclose. The more a physician knows about the patient the more likely it is that the dialogue will satisfy the patient's and physician's understanding of how much detail to offer.

Regrettably, patients may think that a research study is an opportunity to "cut into line" in the advancement of new therapies. It may be natural for a patient to think: "If the doctor recommends it, it must be helpful". However, if the study is research, it may be difficult to get the patient to understand that either there is no likelihood of benefit in therapeutic terms or the researchers or doctors do not know if there will be any benefit. Since research seeks generalizable knowledge, the benefit may only pertain to future patients based on results of this and subsequent studies.

Case 12: Disclosing the risks of Dilantin to seizure clinic patients: how much to state? (Veatch et al., 2010, p373-374).

"Physicians in the Seizure Disorder Clinic of an East Coast Hospital were in the process of developing an information sheet that would be provided to adult patients receiving a common medication for epileptic and other seizures. They set out to explain in lay language the benefits and risks of the medication and alternative treatments. The group preparing the information was committed to providing information to patients as background for their agreement to

recommended therapies. The group was concerned, however, that providing too much information could include items that were unimportant to patients, potentially disturbing, or possibly confusing to them.

They had information available from an empirical study done some years ago at the Johns Hopkins Hospital Seizure Clinic and the Walter Reed Army Hospital. The investigators prepared a list of five potential benefits and sixteen possible risks of the drug. They asked neurologists familiar with the drug which of the effects they told patients about. Then they asked patients which of the side effects they would want to be told about. The study involved both adult patients and the parents of pediatric patients, but only the adult patient data were relevant here. The data on risks were the focus of concern.

The physicians of adult patients, the ones most relevant to the clinic that was writing the information sheet, indicated a range of behaviors ranging from 86% who mentioned gingival hypertrophy (enlargement of the gums) to 3.2% who would mention a small risk of hyperglycemia (high blood sugar.) Only three other side effects were mentioned by at least 50 % of the physicians. These were dose-related ataxia, dose related sedation, and skin rash. Smaller percentages mentioned such effects as hirsutism (hair growth) (45.5%), hematologic changes (33.7%), hepatitis (9.3%), and drug-related mortality (7.5%). The problem was how this list of responses could be converted into items on the information sheet and which should be included.

Before making those decisions, the group also looked at what the patients said they would want to be told about Dilantin. Large majorities wanted to know about each of the sixteen side effects, for example, dose-related ataxia (98.0%), hyperglycemia (77.4%), down to the lowest percentage for drug-related mortality (71.4%).

Given this information, the group set out to write the information sheet. Should they rely on the physicians' views or the patients' views? Since at least some physicians presented each of the sixteen side effects, but a majority presented only four, how would they use this information in deciding which side effects to present to patients? At least some patients would not want to be told about each of the side effects, yet a majority wanted to know about each of them. Which, if any, should be omitted?"

Discussion Questions

What is the relationship between the information sheet and the informed consent document?

Why is the information sheet separate?

Should the consensus of physicians be the guiding norm for disclosure, often called the "professional standard"?

The principle of autonomy grounds the informed consent process. It assumes trust between doctor and patient and between researcher and subject. It extends to the expectation of privacy and confidentiality. The patient should have all information needed to make voluntary informed choice. Withholding vs. disclosing information is a nuance within the consent preparation and within the consent process. The ideal of informed consent rests on true and complete information provided by health care professional(s) and understood by the subject/patient but hard to achieve in practice as the case above illustrates.

"If language is not used rightly, then what is said is not what is meant,

If what is said is not what is meant, then that which ought to be done is left undone;

If it remains undone, morals and art will be corrupted;

If morals and art are corrupted, justice will go awry;

And if justice goes awry, the people will stand about in helpless confusion."

Confucius

CHAPTER 6

Balancing Principles

The three principles of the Belmont Report do not have lexical order. Satisfying the autonomy principle in the informed consent process does not lessen the importance of beneficence and justice. The relationship between promoting a patient's best interest, expressed as beneficence, and the principle of justice in distribution of health care resources should be equally clear to the researchers, the IRB and the subjects.

Autonomy may conflict with the best interest criterion when a patient's goals conflicts with the physician's best professional standard of care opinion. The physician will naturally want to do all possible to serve the medical interest of the patient. Choice among alternative therapies may mean different things to doctor and patient. Moreover, in the U.S. third party payer influence can be significant. If the drug or therapy is experimental, insurance coverage may be limited or absent.

Treatment Option or Pharmacological Wager? (Boyd, 2013)

A 21 year old male (JB) had severe pain in his back and side and a confined rash along the left side of his spine. Doctor at a walk in clinic diagnosed Shingles. The patient had chickenpox at age 6 months, and Shingles is a recurrent herpes zoster virus infection (the same virus which causes chickenpox). JB was given three prescriptions. One prescription for pain, and two formulations of acyclovir, a standard anti-herpes virus drug, one in tablet to be taken by mouth, the other in an ointment to be applied to the rash. The oral form was available in generic version for about $40.00 and the pain medication was similarly priced. The ointment however was $800.00 without prescription insurance ($200.00 with insurance). Having insurance coverage on his mother's policy and no chronic illness, JB lacked prescription coverage, and called me for advice (I am his grandmother). The pharmacist informed us that the oral antiviral was usually sufficient without the ointment. After consulting with the pharmacist he elected to go with the oral formulation without the cream.

As we were leaving the store, JB turned to me and asked why the same drug in pill was cheaper than in the cream. The answer is simple. The oral drug has outgrown its patent restraint whereas the cream is still under patent. Fortunately this case ended well. He cleared the infection within 10 days. This is a simple case where everything worked out well but it could have been much more serious.

Suppose that the same young male had leukemia rather than Shingles. While pharmacological companies clearly are for profit firms with boards of directors and investors to satisfy they are also entrusted to develop useful drugs to treat people when they are ill. Patent legislation assures the company will recover their investment but it refrains from setting a ceiling on profit. All over the world there are people with treatable illnesses. How many of them simply cannot afford the patent price of their treatment?

Nations exist to protect its people. And countries with a national healthcare system allocate treatment on a variety of policy standards. The United States is the only developed country that still struggles to justify to its citizen's universal healthcare. Progress on this issue is painfully slow being hostage to political contest of will to power more than compassionate regard for the people who entrusted them with such power.

What reasonable answer should we offer to any person with an illness that we can treat when such treatment is only available if insured or the patient can afford the medication? Regrettably there are strident voices that either blame the sick for their condition or turn a blind eye saying work hard and you can afford treatment. Such answers risk prejudice in the direction of social worth rejecting claims of those in need as a consequence of their free will actions. A corrective in perspective would come from the view that every person is the product of a birth lottery meaning no person selects in advance their genetic family or their unique capabilities. The preferable alternative is to say that every sick person counts as person whose dignity requires access to medical care. To offer everyone treatment means all workers contribute so that all have access. If everyone is covered and eligible for care it will be necessary to limit healthcare expenses by collectively doing what the insurance companies do currently: negotiate what they will pay for a given drug. If the nation sets prices through such negotiations it would be reasonable to expect some profit limits in the current patent system. Collective accountability and responsibility to fund health care for all would avoid expensive emergency treatments and may in time save health care investments so that universal access is cost effective and sustainable.

The case of Shingles raises a couple additional points. The younger part of the population does not expect to get sick and gamble that they don't need insurance or prescription coverage. Age does not seem a guarantor against this exceptionality perspective. People overeat, skip physical conditioning, smoke, drive at excessive speeds, and seem genuinely shocked if they develop hypertension or are injured in a car accident.

Knowing and recognizing our vulnerability to unexpected illness or need of medical care is an essential step in using healthcare as a trust and not a gamble token. In a capitalistic society that prizes individual freedom over the common good it is easy for the big pharma companies

to set prices as high as they like because they wager a family member will love the patient enough to find the money for treatment. The people who set these policies are sure they get coverage and will not be in need but they may be self-deceived in their assessment of job security and or their individual health status. Until the patient that is a stranger has the same moral claim to care as their beloved family member or oneself, the struggle for universal care is likely to continue.

The most dedicated advocate for individual freedom should see that universal coverage is good for them in case they needed it but that turns out to be a difficult lesson. I have worked for 40 years and had insurance deducted from my wage like taxes and fortunately never been unemployed and thus uninsured. I do not think I am special in this respect but have been privileged not by merit as much as by chance.

If my grandson had needed the expensive cream I could have afforded it, and I let him decide.

Despite the simplicity of the case it has haunted me because his situation could have been much worse and the medicine needed unaffordable. What docs a mother say to a child when he is sick and she cannot afford the medicine? What child deserves to suffer? Sadly, many do.

Ethics offers reasoned discourse on issues that concern the wellbeing of persons. Health is a precondition to human flourishing and as such deserves the status of a human right. It may be open to question what degree or extent of investment is necessary or what degree of health can be attained for everyone. Decisions about strategies and quantitative methods of allocating health care resources ought to emerge from engaged civil conversation within the whole community. The system is complex as are the patients who are persons. If allocation is according to need it is clear that some will receive more than others simply because the need is greater. We should not resent that some folks will need more expensive care, but rejoice that we are well and do not need it. If each person is given a voucher for x value of coverage, and their medical needs exceed that allotment, it seems that the suffering is merely delayed rather than addressed as a human need. More reasonable is the notion that disease categories have a standard of care that is given to everyone with that disease, where ceilings can be set in treatment based on life years gained, risk-benefit assessment. Limits would be set by necessity. Futility rules would be reasonable when a treatment fails to alter the progression of the disease or its outcome.

It is unsustainable to have a maxim such as, "do everything possible for everyone, everywhere". Such a maxim would bankrupt any nation. Therefore procedures and treatments would be offered according to need and an expected outcome in some quantifiable way. A quantitative approach with clear criteria for efficacy should be used to decide what expense to invest to

promote the flourishing of the patient with a wide lens view of what we can sustain if everyone with a similar condition is treated equally.

I propose that the grounding for such an allocation within a universal coverage policy would reduce cost of care and improve overall healthcare statistics in my country. Every patient is a person whose dignity is due respect. I find it easier to forgive the invincibility and self-deception of a person 21 years of age than a 51 year old. Decades of life offers us enough experience that we should learn that we too can be sick, dependent on the care of strangers, at least enough to enact safety nets for all. Dignity is a quality we ascribe to human beings and it is a grave injustice to ignore it.

Justice in the distribution of expensive or scarce medical resources may limit the autonomous choice of the patient: a person may elect an organ transplant without one becoming available. As technology increases, with attendant increases in quality and quantity of life, tensions may become apparent among principles. When is treatment futile? Is the determination made experientially in medical practice? What impact does that have on patient choice? The element often missed is that autonomy conflicts with justice when decisions are made entirely at individual level rather than within the context of the community.

If you found a difference of perspective or opinion in the three case studies in this section within a dialogue group, imagine what an IRB with a dozen or more people experience. All IRB members receive training on the principles and oversight of human participant research, are regulated by the Office for Human Research Protections (OHRP) and try to work for the benefit and good of both research progress and human protections. Regulatory oversight can be burdensome especially where multiple institutions are involved. Whether a centralized IRB is a better paradigm remains to be seen (Emanuel et al., 2004).

CHAPTER 7

Misconduct in Clinical Trials

7.1 VIOXX

An interesting example is the case of Rofecoxib, the generic name for Vioxx. The drug was withdrawn voluntarily in 2004 by the manufacturer due to safety concerns of an increased risk of cardiovascular events in patients taking the medication. Merck developed and manufactured the drug Vioxx as a non-steroidal anti-inflammatory drug to treat acute pain. The drug targets the enzyme COX-2 which is active in inflammation and pain. The drug was approved and released for general use in 1999. The drug was popular and marketed in more than 80 countries, producing $2.5 billion in sales in 2003 alone. It is estimated that 60,000 people died of complications, heart attack or stroke, as a side-effect of taking Vioxx.

In 2008, Joseph Ross at Mount Sinai School of Medicine, New York, published in *JAMA* about the guest authorship and ghostwriting practices of Merck in promoting Rofecoxib/Vioxx (Ross, et al., 2008). Merck employees worked to prepare manuscripts and recruit external academically affiliated investigators to be authors, who were often first or second author on the paper. This case study review demonstrates clinical trial manuscripts were authored by sponsor employees but often attributed first authorship to academically affiliated investigators who did not always disclose industry financial support (Ross, et al., 2008).

It is important to know that when Merck asked for approval from FDA in 1998, the drug had been tested in 8 separate studies on 5,400 subjects. Wanting to show that Vioxx was better tolerated than other painkillers in the gastrointestinal track, a comparison study began in 1999 with 8,000 participants. Half got Vioxx and the other half naproxen. The data and safety monitoring board (DSMB) looked at study results near the end of 1999 and Vioxx patients had fewer ulcers and less gastrointestinal bleeding than patients taking naproxen, suggesting the drug would be preferable. However at the next DSMB meeting, 79 of the 4,000 taking Vioxx had serious heart problems and some died, compared with 41 taking naproxen. The numbers were small and the DSMB continued to watch. In December it was clear that those taking Vioxx had double the risk of serious heart problems compared to the naproxen group. It was not clear if Vioxx caused the higher heart problems or if naproxen like aspirin was reducing it.

Between 2002 and 2004 more and more cases of cardiovascular problems occurred in patients taking Vioxx. Merck withdrew the drug in September 2004, by which time an estimated 20 million

U.S. citizens had taken the drug. To avoid the personal-injury lawsuits of some 47,000 plaintiffs and about 265 potential class-action cases filed by people or family members who claimed the drug proved fatal or injured its users, Merck announced in November 2007 they would pay $4.85 billion to end the lawsuits, one of the largest drug settlement to date (Epstein, 2005).

7.2 TUSKEGEE SYPHILIS STUDY

Much has been written about the Tuskegee syphilis study where the participants were not given penicillin when it became the new standard of care.

The study was originally entitled, "The Tuskegee Study of Untreated Syphilis in the Negro Male." The sponsors were the Public Health Service (PHS), the Tuskegee Institute, the Tuskegee Medical Society, and the Macon County Health Department in Alabama (Jones, 1993, p. 7). The study was designed to study the natural progression of syphilis. There were elements of deception and social pressure in enrollment, lack of transparent informed consent in what is clearly in retrospect a vulnerable population. Issues of voluntariness of participants, informed consent, and public trust in the conduct of research and the use of results emerge and linger in the minds of many people.

The attraction of the population chosen for research was the high prevalence of syphilis. Nurse Eunice Rivers, a black woman graduate of the Tuskegee Institute, was the coordinator of the study. She set up transportation, organized clinics, and served as contact for those enrolled in the study. She was the primary recruiter because she had access to the local population. The Tuskegee Institute agreed to participate as a means of training and employment for its doctors and nurses (Jones, 1993). The men in the study were told they were being tested for "bad blood" which in local use meant a variety of diseases. They were not told they had syphilis or told what it was or how it was transmitted. They were given arsenic and mercury in a minimal course of treatment considered the standard of care at that time. The study was extended so that the men would be examined periodically until their death. An autopsy would give doctors a chance to track the complete course of syphilis left untreated (Jones, 1993, p. 132).

The men got more clinical care than they would have outside the trial. Even the placebo group got iron and aspirin. The deception was that the regular spinal taps were presented as "special free treatment" which had no therapeutic value but provided samples for tracking neuro-syphilis. When penicillin became standard treatment for syphilis in 1953, the study continued without making the antibiotic available to the men in the study.

Reports on the study were given at conferences while the Nuremberg Code and Declaration of Helsinki were being composed without any ethical question or objections raised (White, 2000). In the late 1960's a PHS physician working in San Francisco questioned the study and PHS convened a panel to decide if the study should continue. It affirmed continuation. Then in 1972 a

reporter for the *Washington Star* wrote an article, entitled "Human Guinea Pigs: Syphilis Patients Died Untreated" and the nation and world knew. The experiment ended 40 years after it began (20 years after penicillin had become standard treatment) (White, 2000).

7.3 MALARIA TREATMENT OF SYPHILIS

The history of therapeutic interventions in diseases such as syphilis in the 1920s to 1950s lacked the accuracy and precision of today. In a separate study, Matthew Gambino examined the treatment of neurosyphilis by injecting patients with malarial parasites to induce a high fever hoping to kill the syphilitic spirochete. The study was done at St. Elizabeth's Hospital, a federally funded facility in the District of Columbia. The therapeutic approach began in the U.S. in 1922. The same therapy was used in Western Europe and considered one of the most important advances in modern medicine. Malarial fever therapy raises ethical questions: What would a favorable risk benefit ratio be? How could informed consent be obtained especially if the patients arrived at the hospital in an advanced stage of neurosyphilis? At the time doctors felt they were doing their duty to try innovative even experimental procedures on patients in seeking a successful treatment. Many, if not all, of the patients at St. Elizabeth's were mentally and cognitively compromised, which made the consent issue more difficult, if not questionable. Was admission to the hospital a form of de facto consent? Were relatives asked to provide surrogate consent? What if the patient had no known relatives? The introduction of penicillin therapy for syphilis marked the end for malarial fever therapy although there is evidence that the malarial treatment continued until about 1952–1953 (Gambino, 2015).