RECONCEPTUALIZING THE ETHICS OF PHASE 1 PEDIATRIC CLINICAL TRIALS IN ONCOLOGY

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ABSTRACT

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Phase 1 clinical trials continue to present bioethical challenges in pediatric practice, and pediatric oncology has developed as a subspecialty in part due to a particularly robust research culture. In this project, I explore continuing ethical challenges and call the commonly accepted notion of research as standard practice into question. I suggest that therapeutic misconceptions obscure deeper ethical questions about just how much sacrifice current children can reasonably be asked to endure for future generations and how much and what should be done in the name of maintaining hope near the end of life. It is my contention that phase 1 trials are not the best way to cope with impending death and often require parents and children to give up meaningful experiences for medical heroics.

To examine my hypothesis, I first consider the history of pediatric research ethics with a special focus on the Ramsey-McCormick debate and current federal regulations. Finding little help here, I then turn to the relationships among parents, children, and physicians to discover whether phase 1 trials in their current form can be justified based on the obligations professionals and families have to one another. I conclude that phase 1 trials do not constitute a reasonable way to meet interpersonal moral obligations and represent an impoverished view of medical care at the end of life.

Having argued against phase 1 trials in their current form, I then consider a possible alternative, arguing for hospice care as standard care and for a clinical innovation paradigm. A

clinical innovation paradigm permits physicians to try novel interventions when standard therapies fail according to individual patient needs. At the same time, clinical innovation requires the prioritization of hospice and palliative care for seriously ill children. Although any change will be difficult and requires further analysis, I contend that a clinical innovation paradigm constitutes a better ethical alternative compared to more traditional protocol-driven early phase trials.

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Introduction

While there have been a plethora of debates regarding children in research, difficult questions remain unanswered, and there is a particularly acute conundrum when research involves extremely ill children. In these cases, early phase trials are seen by patients, parents, and physicians as both potential therapies that may be the proverbial "silver bullets" in beating vicious diseases and as research projects that can contribute to the care of future patients. Although clinical trials occur in many different pediatric settings, pediatric oncology as a subspecialty is unique. This field has advanced in recent years primarily through a system of standardized research and treatment protocols, administered by the Children's Oncology Group (COG), in which children who are diagnosed with cancer anywhere in the country can be enrolled in specific trials and their clinical data made available to other clinicians via national databases. COG network hospitals systematically integrate standard treatment with participation on research protocols in a more routine fashion than anywhere else in the medical world because COG considers participation on research protocols as standard care. Additionally, many practicing pediatric oncologists are involved in research, more so than in other subspecialties. COG explains on the organization's website:

> It is important to understand that clinical trials are standard practice in cancer treatment for children, adolescents and young adults. While less than five percent of adults with cancer are enrolled in clinical trials, 60 percent of patients under age 29 diagnosed with cancer are enrolled in trials. ("What is a Clinical Trial?," n.d.)

This fusion between clinical practice and research creates an environment where questions about research ethics are even thornier than usual.

Early phase studies are particularly concerning because their primary purpose is not treatment but establishing dosing guidelines to minimize toxicity. As COG explains:

> Phase I studies are the most basic of clinical trials. Here, drugs are tested to evaluate the dosages of the treatment, and how often the treatment can be administered (maximum tolerated dosages, MTD). As it is unknown whether the treatment will be effective against a particular disease, people with a variety of diseases [cancers] are enrolled. Drugs are given at gradually increasing dosages until there are unacceptable side effects (dose-limited toxicities, DLT). ("What is a Clinical Trial?," n.d.)

Thus, the success of a phase 1 trial does not depend on whether patients are successfully treated, as children with different cancers for which the study drug may or may not prove efficacious can enroll depending on the research protocol. The sole purpose is to determine dosage and dosing schedules for future studies. Though efficacy measures are included in some phase 1 investigations, they are not the primary purpose of those trials. Investigational agents that are deemed sufficiently safe are then further tested in phase 2 and eventually phase 3 studies to determine whether they are truly effective for a particular disease process and how they compare to drugs currently in use, respectively. The FDA reviews all drug approval applications while considering efficacy, safety, and manufacturing procedures.

However, some patients may, by happy accident, benefit from early phase studies. Consider a recent newspaper article from May 2015 that reported "mind-blowing results" in an early phase clinical trial. Dr. Giselle Sholler at the Helen Devos Children's Hospital in Grand Rapids, MI revealed that three children who were diagnosed with incurable neuroblastoma are now long-term cancer survivors due to their participation in a phase 1 trial of new drug

Difluoromethylornithine, otherwise known as DMFO (Thoms, 2015). To be fair, DMFO is not actually a new drug, unlike many phase 1 investigational agents. It has been used for years to treat West African sleeping sickness, a disease involving the same gene as neuroblastoma, and is prescribed in cream form to women experiencing excessive facial hair growth. So, professionals have years of experience with the drug. At the same time, any new use of a drug carries with it the possibility of unforeseen consequences, especially when dealing with already vulnerable, critically ill children.

But, putting talk of risks to the side, the headline is not tentative in the least and conveys only unbridled optimism. Interestingly, "mind-blowing" has two very different connotations in this case. Most people probably would focus on the term "mind-blowing" as meaning extremely significant or undoubtedly good. In this case, the results experienced by a few children are "mind-blowingly" good. However, "mind-blowing" in this case may be more akin to unexpectedly good or significant. Knowing that no one had used DMFO for neuroblastoma before and that the children in the trial had already failed multiple other treatment and experimental regimens might lead one to believe that what is "mind-blowing" is that it worked at all- as in, researchers, parents, and patients should not have expected the results in question.

There is no mention of just how improbable such results are, even though the full journal article mentions that only three children (presumably the ones included in the article) out of eighteen experienced long-term non-progression. Additionally, the study was a dose escalation study where three-subject cohorts were given increasing doses of DMFO as the study continued, meaning some subjects received substantially lower doses of the drug than others (Saulnier Sholler et al., 2015). The primary findings in the study included dosing guidelines and predictive factors. Although the newspaper article does point out that scientific significance has not yet

been achieved, DMFO sounds like the miracle cure for which many children with incurable neuroblastoma have been waiting. As Sholler herself says, even after she urged caution in interpreting the results, "It's great for the world to know kids with neuroblastoma have another option. No one has ever used DFMO with neuroblastoma before," (Thoms, 2015).

There is clearly a difference between the media's portrayal of this phase 1 trial and the actual study results in question. Obviously, the media is apt to take things out of context and are primarily concerned with generating reader interest, not expounding on the finer details of scientific practice. Yet, even bearing this caveat in mind, the tension between research and clinical practice is overwhelmingly palpable in the newspaper article. The reader is led to believe that DMFO has been game-changing clinically; however, Sholler cautions that the results cannot yet be considered statistically significant.

Here, we have a collision between how scientists define significance and how parents, and often physicians, explain a rare, exceptional clinical event. It seems odd to the lay person to insist results are not yet significant when three children have become long-term survivors. True, they are the only survivors out of eighteen total children, but their parents are understandably grateful that their children are among the lucky ones. When parents enroll their children in these early trials, surely they do so hoping for just this kind of miraculous clinical outcome. Not to mention, phase 1 trials are often argued to be therapeutic and therefore permissible on the grounds that a few children might benefit, even indirectly, from participation. Sholler, of course, refers to the fact that scientific significance has not yet been achieved, which really means it is still unclear whether DMFO actually works long-term for many children. The three children cited in the article have survived between two and four years with minimal progression and symptoms after their neuroblastoma was resistant to other treatment regimens, but data from

additional participants is necessary to determine if they are lucky outliers or part of a more significant statistical trend. It remains to be seen whether DMFO is merely promising for a few or if it really is game-changing.

Yet, Sholler's statement about now having new options for children with neuroblastoma demonstrates that she, along with most other physician-researchers, has not teased apart the differences between significance in research and a "mind-blowing" clinical exception. Thus, the article leaves the reader quite confused over just what the goals of the trial were. Once the newspaper article labels DMFO as even potentially game-changing, readers begin to think of it as therapeutic rather than under investigation. Not to mention, parents, children, the public, and physician-researchers themselves are quick to impute therapeutic intent whenever there have been unexpectedly good outcomes. On the flip side, the article also reveals that sometimes phase 1 trials may end up being therapeutic even when not expressly intended. No one can deny that three children with resistant neuroblastoma are now enjoying longer lives.

Confusion over the distinction between medical therapy and scientific research is not new. The term "therapeutic misconception" (TM) was first coined by Applebaum and colleagues in a 1982 study involving psychiatric patients who consented to clinical trial enrollment. Immediately after giving consent to participate in one of two trials, participants were interviewed and asked about their basic understanding of the research and related study procedures. In one of the two trials, the clinical investigators gave potential participants what would be considered sub-standard information in which procedures were not correctly described or even discussed at all. In the other trial, prospective participants were given high-quality information comparable to what is legally mandated by institutional review boards (IRBs). Applebaum and his team were not involved with investigators' decisions about information provision. Unsurprisingly,

Applebaum et al. found that subjects who received sub-standard information were confused about the nature and purpose of research. But, the participants went to great lengths to fill the gaps and speculated that the study procedures would still have therapeutic intent. That is, there was a strong tendency to assume that physicians offering enrollment in the trial had therapeutic aims, even if they also were concerned with aggregate study results.

Even among those participants who had completed the in-depth, high-quality consent process, there was misunderstanding about what randomization meant and how it would impact the treatment they received, how and why they might be assigned to a placebo trial arm, and what it meant for a study to be double-blind. In many cases, participants continued to believe that their trial arm assignment and the treatment provided would be primarily determined by their clinical needs rather than the research protocol (Applebaum et al., 1982). This observed therapeutic misconception can be defined as a state that "exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial" (Henderson et al., 2007). Basically, TM is the conflation of research goals with the goals of clinical care.

While clinical care is designed to help the individual patient, research is designed to contribute to general knowledge. Any ancillary clinical benefits that accrue to individual participants are happy side effects but not the overarching goal. Thus, in the phase 1 trial of DMFO, the trial was a success because DMFO was found to be tolerated without unacceptable side effects at certain doses by most participating children, not necessarily because three children happened to survive. Yet, the newspaper article leads everyone to believe that what is significant

about the trial is that three children survived. We can clearly see the continuing influence of TM today when these sorts of articles appear in the media.

Since Applebaum and colleagues first wrote about TM, there have been many proposed responses to the ethical uneasiness therapeutic misconception engenders. However, these responses have by and large failed to improve the situation. This is likely because researchers have not conclusively resolved major moral questions about the use of current patients for the benefit of future patients and the tension between medical progress and the best interests of individuals. The problem is not that TM exists but that trying to ameliorate it allows us to ignore the more basic questions related to children in research. Even if TM was not an issue in phase 1 trials, we would still need to ask the more basic question, "Is it even ethically acceptable to enroll critically ill children into a phase 1 trial that is mathematically unlikely to help them while maintaining a veneer of therapeutic intent?" Here, I utter a resounding "No." The aim of the present project is to unpack the underlying arguments used to justify pediatric phase 1 trials by looking in turn at historical arguments and national guidelines about children in research, examining the relationship between parents and children and their moral obligations to one another, analyzing physician obligations and relationships to parents and children, and considering ways to allow both research and clinical care obligations to be met if in fact they can be met simultaneously. Importantly, I argue that early phase research involving children can only be deemed ethically acceptable if it becomes truly clinically-driven rather than protocol-driven in nature, including the recognition that palliative care constitutes standard care at the end of life. The present state of affairs has become complicated because research and clinical practice have been combined. Thus, they must be separated to some degree if we ever hope to resolve the subsequent ethical tension.

In order to understand how we have arrived at our present state of affairs, it is first important to look back and analyze the historic debate over whether or not to include children in research. In *Chapter One*, I examine the roots of pediatric research ethics by first analyzing the birth of research ethics more generally. Many of the ethical questions pertaining to children in research have their genesis in the initial codes and formulations promulgated by the developing research ethics community. This chapter covers the Nuremberg Code, the Declaration of Helsinki, and Henry Beecher's now famous exposé on American research practices circa the 1960s. Particularly important themes that will recur include the necessity, but not sufficiency, of consent, the impact and potentially coercive nature of social values and beliefs on research participation, and the difficulty of balancing risks and benefits when children have few options for treatment outside of research. Through historical analysis, I show that major questions about experimental treatment and the line between research and treatment should not be thought of as past problems but as current problems in new contexts.

In *Chapter Two*, I critically examine the history of children in research and the now famous debate between Richard McCormick and Paul Ramsey over children's inclusion in non-therapeutic research projects. I suggest that McCormick's interpretation of parental consent as valid proxy consent for children to engage in possibly high-risk research projects is problematic at best. Furthermore, placing a moral requirement on children to participate in any type of research is fraught with difficulty. On the other hand, Ramsey may give us insights about early phase clinical research that have heretofore remained unexplored, despite his sole focus initially on non-beneficial research.

I then examine the current federal research regulations and discuss how phase 1 research is classified and justified from a regulatory perspective. I particularly focus on the fact that

classifying phase 1 trials as potentially beneficial to children allows for children to be put at significantly increased risk than is possible in non-beneficial situations. The notion that a phase 1 trial might, no matter how improbably, be curative allows risks to be balanced against potential cure in risk-benefit determinations and tilts the scale toward allowing much greater risk than would be allowed otherwise. Finally, I discuss the increasing impetus to more closely integrate research and practice in clinical settings, arguing that as research and practice become more united patients have fewer choices and can no longer be sure of their physicians' primary loyalties. This state of affairs undermines Paul Ramsey's (2002) insistence on the "covenant of loyalty" between physician and patient- an idea that continues to figure in the reasons that people give for trusting their physicians with life and death matters. These discussions demonstrate that the conflict between the perceived need for progress and the needs of today's patients is far from resolved, especially when it comes to children. How much can they be expected to sacrifice for others when they will likely never realize the individual or collective benefits of their sacrifice? Here, I argue that it is important not to view children as merely potential adults whose interests can be discovered by grafting adult values and beliefs onto them.

Having established the lay of the landscape, I turn in *Chapter Three* to the relationship between parents and their children because it is often used to justify phase 1 trial enrollment insofar as there is a general belief that parents have the right to make decisions for their children. The hospital environment, where a signature on a signed parental consent form makes the difference between enrollment and non-enrollment in a trial, requires us to consider what does or should empower parents to make decisions for their children and the grounds for parental rights more generally. In order to explore whether parental consent can be a sufficient reason for enrolling children in early phase research, I analyze the complex roles parents and children have

in society and examine the moral obligations each has to the other. I argue that parents have four primary obligations to their children, including protection, love, identity formation, and facilitating autonomy. Children also have social roles to play, though they do not have moral duties in the same way as their parents do. Children are supposed to be obedient, care-free, and future-oriented. Most importantly, they are supposed to grow up.

In *Chapter Four*, I consider how models of parental responsibility look practically at the bedside. Critical illness forces parents to re-evaluate their duties and children to take on different social roles. Enrolling in a phase 1 trial, especially when one believes it be potentially therapeutic, may seem like the best way to protect, love, and insure the survival of one's child. Children who are old enough to perceive their parents' hopes may feel that enrollment is the best way to fulfill their own social obligations to their parents. However, I call these assumptions into question by examining the compulsion parents feel to enroll their child and the losses children and parents suffer when they are denied the opportunity to shape their lives in accord with their capacities through end-of-life planning and care. Finally, I consider how parents might fulfill their roles and discharge their responsibilities to their children without necessarily pursuing every medically aggressive option at the end of life. It is my contention that parents need not and oftentimes should not enroll in phase 1 trials as a mechanism for fulfilling their obligations as parents.

In *Chapter Five*, I consider the arguments made by and about physicians and their professional roles as potential justifications for early phase research with children. Physicians and researchers have unique and distinct roles, and there are conflicts of interest whenever these roles intersect, though these conflicts often go unacknowledged. In order to better understand physicians' obligations, I first look at the duties assigned to physicians by society at different

times in history with a special focus on the role of pediatrician as co-fiduciary of a child's interests. I emphasize the tension between the physician's role as fiduciary of a child's health-related interests and the autonomy necessary for parents to act as fiduciaries of all a child's relevant interests when making treatment decisions. Additionally, I examine what it means to be a fiduciary in pediatric medicine rather than a guardian of autonomy when caring for competent adults.

Then, I consider a series of current arguments made in favor of joining clinical practice and research, including the appeal to the indistinguishability of research and practice, clinical equipoise, the notion of scientific or intellectual duties and the adoption of a utilitarian ethic valuing progress above most every other aim (i.e. the need for pediatric research trumping any inconvenience for today's patients), and contractual versus covenantal medicine. It is my contention that none of these arguments holds up to scrutiny upon close examination. The role of physician is distinct, and enrolling one's patients in phase 1 trials is not a way of substantially fulfilling one's professional obligations. Here, it is important to consider how a variety of conflicts of interest can contribute to errors in judgment about the efficacy of clinical trials. Finally, it is crucial to unpack what practicing medicine in the face of critical illness means and whether phase 1 trials can truly provide the kind of hope the medical community and general community expect from them.

After considering various arguments in favor of pediatric phase 1 trials, I turn in *Chapter Six* to a potential solution to the current quagmire. To my mind, research and clinical practice will always be in conflict to some degree. The best way to solve the ethical problems is to make early phase research more truly clinical in nature. Early research may need to become more akin to clinical innovation than to traditionally protocol-driven projects. The widespread use of the

randomized control trial (RCT) has given rise to the notion that any other method of evaluating efficacy or generating knowledge is somehow inferior or more prone to error. I challenge this argument and counter that physicians still know a great deal through different types of research, including retrospective data collection. While the Food and Drug Administration's (FDA's) drug approval requirements certainly drive some of the emphasis on RCTs, the scientific community has also been complicit in whole-heartedly embracing the current paradigm. Using a conceptual scheme based on clinical innovation would allow physicians to provide investigational drugs when other treatments had failed and when they believed the drugs would not unduly burden children rather than according to a standardized protocol. Medical therapy is by its nature individualized, and clinical innovation allows for individualized care even when it involves new drugs or procedures.

In the final analysis, I argue that there is little reason to believe the inclusion of children in phase 1 trials, at least in their current form, is ethically permissible. The default position that clinical trials are at worst non-harmful and at best good medicine is untenable. If we as a society are going to "sin bravely" in the words of Paul Ramsey (1976, pg. 21) for medical progress, we ought to do so only in the most clinically-oriented, risk-averse way possible. At the very least, we should not deceive ourselves into believing that early phase research is really clinical beneficence and not a true sacrifice at the end of life. Perhaps our most ethically problematic move was to assume that because we believe research is needed it must automatically be made to coincide with the ethics of clinical medicine. Indeed, the two turn out to be very different types of endeavors with different moral requirements all together.

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Chapter One

The Early History of Research Ethics

Medicine continues to have an uneasy relationship with research. On the one hand, the public anxiously waits for new treatments aimed at curing ever more vexing diseases, and physicians dream of providing those sought-after cures. On the other hand, physicians desire and the public expect them to provide individualized care to today's patients. As medical research becomes more embedded in clinical care, questions about the boundary between research and practice, the dual responsibilities of physician-investigators, and the selection of research subjects also require increasingly complex answers. Indeed, evidence-based medicine has become the new gold standard for practitioners, and the RCT design has become the go-to construct for determining which medical treatments are most effective. All physicians are expected as a matter of professional integrity and competence to provide high quality care based on new information gleaned from medical research, increasing the value of and interest in medical research participation. It is understandable that an increased focus on medical research generally provides individual physicians with a strong impetus to participate in research themselves while continuing to perform customary patient care duties. Thus, the line between research and practice now becomes finer for many clinical practitioners, and physicians' obligations to patients qua patients and as research subjects overlap to a historically unprecedented degree.

Nowhere is there more consternation over research and practice than in pediatrics where patients cannot yet decide for themselves. In light of the ever-increasing fusion between medicine and research, it is necessary to take up the question of children's participation in

research, especially research that involves limited or unknown benefit and serious or unknown risks, once again. If we want to have a clear picture of the present situation, we first need to understand the origins of the regulations we have today and to examine how we got to where we now are. This includes understanding the initial codes of the modern bioethics movement. The discussion is partly to set the stage but also to point out that historical circumstances are not entirely foreign to our own endeavors. While at first these codes appear to have little relevance to the debates we have today about children in research, they serve to highlight some of the fundamental questions that lurk in the background during these discussions. Phase 1 trials are simply the latest frontier, just as those practices in research we see as crude today were at one time considered the next great frontier.

Once this background is provided, we will consider, in *Chapter Two*, the deliberations of the National Commission in the 1970s and the current regulations dealing with children in research, critically analyzing what they allow and disallow and why they prohibit and promote certain kinds of research. Here, we will encounter Paul Ramsey and Richard McCormick and their differing views of what justifies involving children in research. I argue that classifying pediatric phase 1 trials as having the possibility of direct benefit allows significant, not otherwise justifiable, risks to be balanced against an extremely remote chance of benefit. This allows for children to be put at great risk in the hope of a miracle without adequate end-of-life provisions. When we accept the remote likelihood of benefit, Paul Ramsey's injunction to "sin bravely" (1976) proves useful. New measures are needed to protect children who may be sacrificing at least some of their interests for the greater good. Finally, I think it wise to consider newer voices emerging in the larger research ethics debate, as they are both pushing the field in new directions and bringing everyone back to the foundational questions that gave rise to the initial debates over

children in research. It is important to step back and consider whether medical progress is a moral duty or simply one of many goals in the medical profession.

Before Nuremberg

The ethics of medical research is thought of as a comparatively new subfield within the larger tradition of medical ethics. While codes for physician behavior have existed since ancient times, codes governing the behavior of medical professionals in research did not come to the forefront until the 1950s, 60s, and 70s, as the modern bioethics movement was born. This is not to say that guidance about physician conduct in research did not previously exist, but it received little attention in the United States. As early as the 1860s, Claude Bernard wrote about both the necessity of experimental medicine and the maxim that patients should never be purposely harmed in pursuit of knowledge (University of Texas Medical Branch at Galveston, n.d.). By 1900, Prussia promulgated official regulations for the conduct of non-therapeutic research and insisted on informed consent for therapeutic procedures (Vollmann and Winau, 1996, pp. 1445-46).

The most detailed pre-Nuremberg guidelines actually emerged within Germany in response to an enthusiastic embrace of scientific medicine. Before the complete Nazi takeover of German society, experimental medicine was already eliciting public concern and protest, and physicians were routinely required to conduct research in order to receive a medical degree or advance substantially in their careers (Weindling, 2008, Loc 1253/41798). The *Reich Circular for Human Experimentation*, published in 1930, provided ethical guidelines for research with human subjects, insisting on subject consent and the special protection of children in research (Weindling, 2008, Loc 1272/41798). These regulations included many of the standards we hold

for research today, focusing on beneficence, non-maleficence, and legally effective informed consent. The *Reich Circular* also required that clinical trials be overseen by leaders with a clear chain of command who would take responsibility for any instances of professional misconduct (Vollmann and Winau, 1996, p. 1446). Presumably, most medical trainees and physician-scientists working in pre-Nazi Germany would have been aware of these regulations even though the Nazi regime obviously did not enforce them in any way.

Germany was not the only country struggling with and responding to deep-seated concerns about the medical research establishment of the day. Sinclair Lewis' 1925 novel *Arrowsmith* captured the realities of working in medical science while trying to fulfill clinical duties. In brief, *Arrowsmith* tells the fictionalized story of Paul de Kruiff, a medical scientist working in the hottest field of the day- bacteriology. Although not a physician himself, Lewis' fictional story relied on his encounters with leading physicians and researchers. The novel's protagonist Martin Arrowsmith is a country doctor and public health officer who is eventually invited to join a prestigious scientific institute. Martin discovers a bacteriophage possibly capable of eradicating serious infectious diseases. His opportunity to test his invention comes during a bubonic plague epidemic on a Caribbean island. But, tragedy strikes when his wife accidentally smokes a cigarette contaminated with the bacteriophage and dies. Martin abandons his two-arm placebo and bacteriophage trial and instead offers bacteriophage to everyone who wants it. The novel deals extensively with the scientific culture of medicine at the time and the competing motives of profit, prestige, and altruism (Markel, 2015). The legacy of *Arrowsmith* endures even today, as the caricatures of the overzealous scientist and the hard-working clinician still strike a chord with readers.

The Nuremberg Code

The first guidance that caused considerable discussion on research ethics internationally came out of the Nuremberg Trials. Because these proceedings were designed to remedy the abuses suffered by Holocaust victims, the Nuremberg Code focused on the necessity of a potential subject's voluntary consent, the protection of research subjects against unnecessary or unusual risks, subject rights and continuing autonomy while enrolled in research, and scientific validity (United States Department of Health and Human Services, 2005). This focus certainly makes sense in the historical context; but, due to this very focus, the usefulness and relevance of the Nuremberg Code is easily questioned. After all, we believe we are far past the horrors of the Holocaust, and any reputable physician involved in research would be investigated immediately (and probably "de-frocked" with all due haste) if atrocities like the previous ones were committed in the name of medical progress. Nuremberg never had the force of international law, and it remains a set of ethical precepts rather than official regulations. Not to mention, the Nuremberg Code provides little guidance on many of the complex ethical issues we face today. For instance, it fails to provide any guidance on when we can do research with children or incapacitated patients. It says nothing about how physicians who are serving both as patient care providers and as researchers should act nor does it say anything about the line between research and practice. Is it, therefore, possible that the Nuremberg Code really has very little relevance to us today?

I argue that two major mistakes can be made in considering the Nuremberg Code's contemporary application and usage. First, it is a mistake to think that medicine was somehow hijacked by the Nazis in pursuit of their goals; and this mistaken assumption has allowed other modern industrialized societies to persistently believe that the tragedies of Nazi medicine could

never be easily repeated. But, the truth is that Nazi research misconduct was very much about professional power and its impact on patients in need. While we certainly place limits on professional authority in light of past experiences, there are still many instances in which physicians are able to use their power nearly unchecked to promote either good or bad ends. Questions about what it means to responsibly exercise authority remain as physicians face new circumstances (Seidelman, 1996). The phase 1 trial is just such an instance of the need to exercise medical authority judiciously. Certainly, the motives are different, but we cannot underestimate the power a physician has when he offers a trial in the service of science to patients who desperately need his clinical expertise and care.

Written documents that emerged from the trials often imply that science was merely society's pawn under the Nazis and that medical research atrocities had little or nothing to do with how medicine was routinely practiced in Nazi Germany (Marrus, 1999, p. 111). Yet, the historical evidence suggests that these doctors were not merely caught up in Nazi propaganda or pressured into conducting these heinous experiments. Racist and eugenic scientific theories had become dominant and normative in Germany and other Western countries even in the years preceding the Holocaust, as evidenced by Nazi atrocities committed against German citizens for non-research, purportedly "clinical" purposes. These interventions included forced sterilization and state-mandated euthanasia of those citizens not considered to be worthy of societal recognition or participation (Marrus, 1999, pp. 113-16). Medicine had in a real sense both responded to political ideology and engaged in the iterative process that further entrenched this ideology in the medical and scientific communities. Hanauske-Abel (1996) has even presented historical evidence that suggests Nazi medicine set its own course based on economic, political,

and scientific realities. The perceived need for certain experiments was used as a sole justification for carrying them out.

Nor were the Nazi doctors alone in conducting dangerous experiments as part of war time efforts. In a famous exchange during the Nuremberg Trials, Andrew Ivy, a United States representative from the American Medical Association (AMA), claimed that nowhere in the United States would one find this sort of egregious research misconduct. But, there were real questions in the U.S. of whether or not doctors had violated the Hippocratic Oath when conducting research with the mentally ill, prisoners, and conscientious objectors during the war. While their conduct did not reach the same levels of depravity and disregard as the Nazis did, it is a mistake to believe that the Nazis were the only ones capable of violating human dignity in the name of science (Marrus, 1999, pp. 121-22). These early codes are important because they remind us that though the Nazis particularly perfected medical research atrocities they did so in a culture that was captivated with scientific precision. The seeds of these research atrocities had been planted in German society before the Nazi takeover.

Secondly, it is irresponsible to think that we have fully and satisfactorily remedied the Nazi atrocities or the underlying issues that led to these events. First and most egregiously, many culpable medical professionals escaped prosecution and also continued working in prestigious medical positions long after World War II ended. In one of many egregious examples, Carl Schneider's (a psychiatrist who participated in the killing of children and collection of many Nazi victims' brains) daughter-in-law published his work on euthanasia as the thesis for her MD degree in 1946. The brains of victims collected by Schneider continued to be examined after World War II and resulted in more than thirty post-war research publications (Weindling, 2008, Loc 1622/41798). In fact, German medical teaching and research institutes continued to hoard

and use Holocaust victims' body parts for research and academic purposes until the 1990s when there was a move to bury the specimens. Only minimal efforts were made to identify victims, notify families, or provide for personal burial (Weindling, 2008, Loc 1656/41798). At the same time, official recognition or compensation was never offered to those victims who did survive or the family members of the deceased. There has been no adequate recognition of the scale of research atrocities. The truth is that we, as human beings and members of a global community, are far from having resolved the dilemmas surrounding Nazi research.

So, what can Nuremberg teach us today, especially when considering research with children? I propose that when we see the behavior of physicians in the Third Reich as more than an aberration and as a potential consequence of overzealous scientific motivations combined with toxic public policies, we can appreciate that Nuremberg should still speak to us today. Many still ask the question of how an entire medical system could be caught up in or even actively participate in a bureaucracy encouraging the complete abandonment of basic patient care principles. As a reminder of the ways physicians and other professionals both openly and tacitly went along with Nazi policies and ideology, a new memorial placed near where the Berlin Wall once stood symbolizes the bureaucratic processes that allow humans to accept evil as a normal part of the world (Annas and Grodin, 2008, Loc 6609/41798). Evil can easily become a part of any human institution, and preventing egregious professional misconduct is a continuing struggle. Without appropriate checks and balances, no country is immune from these horrors. Additionally, no profession is morally immune, even if we believe things look wholly different today. Changing politics and ideologies shape what practices society and professions deem acceptable (Wikler and Barondess, 1993).

Consider the events taking place during the Tuskegee experiments. Over a forty year period, 600 men, their sexual partners, and some of their children were exposed to the horrors of syphilis, even after effective treatment became widely available (Tuskegee University, n.d.). This study, sponsored by the U.S. Public Health Service, involved many physicians and other health care professionals over a sustained period of time along with cooperating regulators. The purported medical need for a study tracking the natural history of syphilis infection combined with dismissive attitudes about the interests of impoverished black men and their families led to one of this country's worst abuses of medical power (Pressel, 2003).

Similarly, sexually transmitted infection (STI) research conducted in Guatemala was horrific, involving the forced inoculation of Guatemalan sex workers, prisoners, soldiers, and psychiatric patients with infectious material. In the 1940s, the role of penicillin in curing syphilis was first being clearly elucidated, and the disease, along with other STIs, was a major problem for the U.S. armed services. Dr. John Cutler, an ambitious young U.S. public health service physician who would be involved with the Tuskegee studies as well and remain unapologetic about his participation throughout his life, developed a grant proposal in collaboration with other investigators to study the treatment and prevention of syphilis and other STIs, including gonorrhea and chancroid. The proposal received funding from the National Institutes of Health (Zenilman, 2013). The purpose of the research study was to create a natural model of human infection and then compare penicillin treatment to other available alternatives to determine which was most effective. Subjects would be forcibly inoculated with infections or exposed through sexual intercourse while being given various prophylactics and/or treatment over the course of the study. It is important to understand that commercial sex work was legal in Guatemala at the time (Zenilman, 2013). Researchers expressed concern about their activities being divulged to

the general public, but they seemed so committed to their scientific objective that they expressed little concern about the impacts on subjects. The conduct of the Guatemalan experiments came to light in 2010 and prompted a debate over continuing problems in research ethics (Zenilman, 2013).

Susan Reverby, the person responsible for unearthing the Guatemala experiments in the course of writing a book about Tuskegee, argued in a 2013 editorial that it is easier to place the blame on a specific person or group of people than to consider the continuing institutional and economic conflicts of interest driving research. Real progress requires us to grapple with the pressures to find a cure for a serious disease and to consider how scientists fall into the trap of believing their special calling is enough to justify ethical lapses (Reverby, 2013). As Kayte Spector-Bagdady, a lawyer and bioethicist working on staff with the Presidential Commission for the Study of Bioethical Issues during their investigation of the Guatemala experiments, pointed out in a 2015 presentation at the Michigan State University Center for Ethics and Humanities in the Life Sciences, there were many academics and clinicians involved in the Guatemalan syphilis research. What should concern us today is the fact that so many people willingly engaged in patently morally wrong research in the service of what they felt were vitally important social objectives. The researchers at times appeared almost glib about their activities. It was simply something that had to be done. Today, we continue to face the pressure to remedy dangerous and intolerable situations through research, but at what cost? (Spector-Bagdady, 2015)

Our society is not immune to the forces that contributed to the wholescale acceptance of Nazi medical standards and the ethical lapses in the Tuskegee and Guatemala cases, including the social prestige of academic science, the belief that scientific knowledge is the best or most objective form of knowledge, and the prioritization of scientific success over individual interests.

One need only pick up a newspaper article extolling the benefits of scientific discoveries or observe how science is often seen as a potential savior for those likely already beyond its help to understand just how much normative power science has in our modern society. Scientific discoveries are still a source of great professional prestige; and in the name of making so-called "objective" scientific discoveries, there is still great pressure to perform experiments that may place today's patients at risk for the good of future patients. Certainly, the U.S. medical research community is a different creature than the Nazi medical system ever was, and nearly all physician-researchers are committed to ethical research that serves the greater good. But, this fact does not mean we can forget the roots of the regulations we take for granted or neglect our vigilance. Changes in research practice and culture require us to pro-actively re-evaluate what constitutes ethical conduct.

Nuremberg will never lose its relevance as long as human beings are charged with wielding medical and scientific power. Even more significantly, Nuremberg should remind us that children have been and are apt to be particularly vulnerable in medical research settings. Children are easily influenced and controlled. They are taught obedience to authority, and they desperately want and need to be accepted by those close to them. Practically, children have very "soft" or even non-existent voices in decision-making, and their needs and interests can easily be subsumed into adults' needs and interests. Children deserve special protection, and their interests deserve priority consideration.

In the context of phase 1 trials, the Nuremberg Code's insistence on the need for voluntary informed consent and subject protection should give us continued pause. Children cannot give their consent; and, despite the fact that parents and physicians have children's interests in mind when making decisions, consenting for someone else is fundamentally different

than consenting for oneself. Additional protections are necessary when a person cannot give consent and are a part of insuring subjects are not exposed to unnecessary risks. The risk of making substantial sacrifices when a child may have little time to live is significant and should be mitigated.

The Declaration of Helsinki

The Nuremberg Code helped to begin an international discussion of research ethics, but it was only the first of several attempts to move the conversation forward. Another code arising from the aftermath of World War II was the World Medical Association's (WMA) 1964 Declaration of Helsinki which was most recently updated in 2013. Focusing on the conduct of medical professionals, as opposed to all researchers, involved in research projects, the Declaration of Helsinki is widely recognized as an authoritative guide for physician-researcher conduct, though it does not relieve physicians of country-specific legal or ethical regulations. It does not dictate any specific conduct on the part of physicians and, like Nuremberg, is more important for its principles and ideals than its practical applications. Despite these challenges though, the Declaration provides a slightly different perspective on investigator obligations, focusing on the need to weigh the good of medical research against the health and welfare of potential subjects. For instance, the Declaration focuses on the need to balance risks and benefits to insure proportionality and elevates the evaluation of risk over the absolute need for informed consent (Ashcroft, 2008, Loc 6742/41798-6774/41798). Informed consent becomes a standard for competent autonomous agents rather than an absolute requirement for clinical research, and this move allows for the inclusion of children and other subjects who are not able to give consent as long as a legally responsible agent (often the parent) provides consent and risks are minimized.

While the Nuremberg Code would have likely prevented any research with children who are categorically unable to give consent, Helsinki allows children to share the burdens and benefits of research when necessary protections to prevent harm are in place. Indeed, by the 1975 revision, the Declaration emphasized the importance of medical research insofar as every current treatment has resulted from previous research endeavors. Proponents argue that it is reasonable to assume a subject should generally be willing to participate in research if he benefits from current treatments, perhaps leading to some ethical obligation to participate in certain types of research (Ashcroft, 2008, Loc 6815/41798). It is only one step more to make the argument that children and their parents have some responsibility to participate in research, assigning moral responsibility to children to contribute to future treatments. This argument continues to have traction today and is often invoked as a reason why seriously ill patients should take on additional burdens from research participation even when they do not stand to truly benefit from the project in question. Children also are enrolled in these trials for the sake of future knowledge. While no one ardently supports mandatory conscription into research, social pressure and a sense of scientific responsibility can give rise to coercive conditions.

The 2000 Declaration was substantially revised in order to address contemporary challenges with varying degrees of success. Most importantly for the present project, the 2000 Declaration states that participants should have access to an independent physician during the consent process to prevent conflicts of interest or duress from dual relationships when physicians are both patient care providers and investigators (Ashcroft, 2008, Loc 6926/41798). In Section B, paragraph 23, the 2000 Declaration states:

> When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or

> may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship. (World Medical Association, 2001)

However, the Declaration also continues to allow standard medical practice and research to be combined. Per Section C, paragraph 28, "The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value" (World Medical Association, 2001). Additionally, in paragraph 32, physicians are permitted to pursue unproven clinical options when all standard treatments have failed, but they are encouraged to make all interventions part of a standardized research protocol that evaluates safety and efficacy (World Medical Association, 2001). Here, the Declaration has introduced an ethical tension whereby the World Medical Association recognizes that patients are vulnerable when physicians act as both clinical care providers and researchers but continues to allow and even encourage research and clinical care to be combined; and, little has been done to remedy this apparent contradiction.

The distinction between research and clinical care has specific implications for research with children. When parents consent to medical treatment, they do so knowing the physician is working in the interests of their child. But, research introduces a different set of priorities and obligations, and those obligations may at times be complementary but can also result in significant conflicts. The Declaration appears to prohibit research that does not offer net benefits to participants, as it requires that patient welfare be the physician's overarching concern (Forster et al., 2001). This requirement makes the status of early phase research that may be more risky than beneficial or research with a relatively unknown risk-benefit ratio morally nebulous.

The most recent revision to the Declaration came in 2013 and did little to address potential conflicts between research and practice, though it does obviously prohibit physicians from knowingly and intentionally harming patients. However, contemporary conflicts between research and practice are highly nuanced and do not generally involve physicians who are seeking to inflict harm on patients or to intentionally sacrifice patient welfare. In these situations, the Declaration offers few solutions and serves primarily to "muddy" the proverbial waters. For example, Mullim et al. (2013) argue that the Declaration prohibits a wide variety of non-beneficial research projects that are crucial to improving medical care but offer no direct benefit to participants. These projects can be low-risk, and it may then be possible to conduct non-beneficial projects without overruling participant rights or well-being.

Overall, I believe that the Declaration has brought a primary conflict between practice and research to the forefront and should remind us that we have not yet put forth satisfactory resolutions to many important questions. The Declaration continues to emphasize that physicians should make their patient's health and welfare their primary concern while also allowing research and clinical care to be combined (World Medical Association, 2013). In the section "General Principles," the fourteenth principle is as follows:

> Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects. (World Medical Association, 2013)

This statement is certainly a praiseworthy goal. But, the combination of research and practice means some patients will be exposed to unknown risks with no possible way to completely insure their welfare. Physicians cannot unequivocally vouch for the benefits or safety of an intervention that has not previously been used or studied. Animal studies are helpful, but perceived risks and benefits do not necessarily translate well into human studies. With principle 14, the Declaration places physicians in an unbreakable bind whereby they are expected to act to promote the interests of their patients while at the same time conducting research designed to prove if an intervention is safe and effective.

Forcing physicians to serve two masters- clinical medicine and science- is more difficult than might first be apparent. If physicians prioritize the welfare of their patients, they may not be able to conduct the kind of rigorous scientific research necessary to answer complex questions. If they choose science over medicine, then they have failed to fulfill the Declaration's requirements. Siding with the Declaration would seem to prevent some experimental practices that are scientifically valid but may result in patients not receiving adequate treatment (i.e. randomization without regard to clinical status, blinding of physician-investigators, etc.). Preventing these practices may mean that patients are enrolled in research with questionable validity, and they are placed at increased risk even when no net benefits to society can ensue. Thus, the question of just how physicians should balance practice and research remains unanswered.

Where Nuremberg insisted on consent as the barometer for ethical research, Helsinki emphasizes the balancing of benefits and burdens- a much more difficult, though necessary, move. In Helsinki, we see the first arguments for including adults and by extension children in research and the prospect of balancing subject's interests with society's needs. In the context of

pediatric phase 1 trials, we have to consider if and why children should be expected to participate in research unlikely to benefit them. This question figures in the debate between Paul Ramsey and Richard McCormick. Helsinki did not provide any concrete guidelines for how we might protect the interests of patients who are engaged in higher risk research possessing a minimal potential for benefit. Finally, Helsinki explicitly allowed for research and practice to be combined, as pediatric oncology has now perfected. But, the question of how to balance competing loyalties and what obligations a doctor cannot cede in the name of science is still vexing. We shall endeavor to find answers in subsequent chapters.

Research in the United States

Both the Nuremberg Code and the Declaration of Helsinki had limited impact in the U.S. after World War II. Questions about ethical research in the U.S have been addressed specifically since the 1970s, largely in response to a now famous exposé published by Henry Beecher in 1966. In his article titled "Ethics and Clinical Research," Beecher documented cases of unethical research at major academic medical centers, highlighting the fact that the United States was not immune from the kind of misconduct thought to be unique to Germany (Beecher, 2001). Beecher was alarmed at the rapid growth of research and the increasing number of ethically questionable practices that were thriving in academic medicine.

Four of the incidents Beecher revealed involved children, with the most prominent example concerning events occurring at a state institution. The events at Willowbrook State School are now one of the most significant historical examples of research misconduct involving children. Yet, in 1981, Dr. Saul Krugman, the researcher who conducted the now infamous experiments at Willowbrook, received the American Pediatric Society's highest honor- the John

Howland Medal. He was lauded for his professional accomplishments and work in pediatric infectious disease (Lantos, 2010, pp. 613-14). So, just what did happen at Willowbrook, and was Krugman's work merely controversial or actually unethical? The answers are unsatisfactory in that there has never been an independent outside investigation of exactly what happened at Willowbrook. Most accounts are based on Krugman's own reports at the time (Lantos, 2010, p. 616). In fact, Krugman published a detailed account of the events at Willowbrook in 1986 as an ethical justification for his and other researchers' conduct, and this account will serve, albeit likely imperfectly, as the historical record here.

Willowbrook State School was completed in 1942; and, after a stint as a military hospital in World War II, Willowbrook began admitting severally mentally impaired children in 1947. There is no doubt that few options or resources existed for the care of these children, and parents who felt they could not independently care for their children were desperate for their placement in therapeutic, at least by the standards of the day, state facilities. By the 1950s, Willowbrook was overcrowded, and hepatitis, along with other infectious diseases, was rampant. Willowbrook staff did attempt to ameliorate the crowded conditions, but New York provided insufficient support.

A 1955 epidemiologic study carried out by Krugman and his colleagues showed that the endemic hepatitis at Willowbrook was hepatitis A and was generally mild and self-limiting. In the hope of creating a vaccine, Krugman and other staff members began admitting a small number of children to a specialized unit at Willowbrook where they were deliberately exposed to the mild hepatitis A strain. As serological testing became more precise, Krugman and colleagues discovered that a distinct strain of hepatitis B also infected children at Willowbrook, and they began exposing children to both mild hepatitis A and hepatitis B strains. Here, it is important to

note that while children generally recover from both hepatitis A and hepatitis B without incident there is an increased risk for later hepatic disease after hepatitis B infection. The risks from planned exposures were not necessarily greater than those faced by children in the institution generally, but the researchers exposed the children deliberately. The researchers deplored institutional conditions but did not first seek to investigate how they might improve those conditions with or without state support. It remains to be seen how a clinical medical solution to the problem would have been implemented or funded at that time.

Krugman (1986, pp. 159-60) described informed consent procedures in great detail and pointed out that Willowbrook implemented a research consent process long before it was standard in U.S. medical facilities. Initially, parents were notified by mail. However, the research team soon began a group consent process where parents first met for a preliminary interview with a psychiatric social worker and then, if interested, received information about the study in-person with the entire research team present. Parents had two weeks to decide about study enrollment and were free to consult with their private physicians about the decision. Krugman also notes that the research protocols were approved by multiple local, state, and federal agencies (1986, p. 160). The Willowbrook experiments certainly generated new scientific knowledge that led to a better understanding of hepatitis infection. But, at what cost was this knowledge obtained? After all, the bottom line was that disabled, disadvantaged children were purposely exposed to illness.

The events at Willowbrook highlight several important moral questions. Most importantly, for our project, the events at Willowbrook raise the question of whether parental consent is sufficient justification for enrollment in potentially risky research (Lantos, 2010, p. 618). Certainly, parental consent is necessary in all but the most special cases (i.e. emergency

research). Willowbrook, however, serves as a reminder that medical professionals bare a responsibility to only offer parents ethically appropriate research options. Professionals cannot operate in isolation when deciding what constitutes an appropriate research option and ought not to take the ability to obtain parental consent as evidence of a research project's ethical appropriateness.

Additionally, I would add that the conditions parents faced if their children were not admitted to the special Willowbrook unit likely made consent a mere formality. Parents had no other care options for their children, so participation in the Willowbrook experiments probably felt like the best and only solution under the circumstances. Refusing a place in the specialized experimental unit meant keeping a child at home. In 1954, Willowbrook was closed to new admission due to overcrowding, but researchers indicated new children could be admitted if they volunteered to be placed on the experimental unit. Investigators claimed they did not mean to coerce parents into participation; yet, parents were in a no-win situation (Ross, 2006, Loc 294/4226). While this situation was not the researchers' fault or even responsibility, it impacted the parents' ability to freely consent and should have been considered potentially coercive. Anytime there are limited opportunities to access medical care outside of a study the potential for coercion exists. Failing to recognize this reality makes truly voluntary consent harder to obtain.

It would be remiss at this point not to mention one other particularly interesting case that Beecher (2001) described in his now famous article because the case touches on the special bond between parent and child and the lengths parents will go to for their children. It will be helpful to keep this case in mind as we consider why parents and children make the choices they do in the face of grave illness. In the eighteenth example of possible research misconduct described, Beecher recounts a case where a deadly melanoma from one woman was transplanted into her

mother. The mother voluntarily agreed to the transplant because she felt researchers might learn something about her daughter's disease process or she might produce antibodies to the melanoma that would prove useful in her daughter's treatment. The daughter was terminally ill before the transplant and died the day after the procedure; her mother went on to develop terminal melanoma from the transplant, dying a little over a year later from the disease (pp. 1358-59). This mother made the ultimate sacrifice even when she knew the chance that she might realistically help her daughter was slim or even non-existent. She desperately wanted her daughter's death to mean something. This story shows how vulnerable parents are when their children are sick. Most reasonable people would not have consented to such a risky enterprise, but a mother does not weigh risk in the same detached way it is often viewed by medical professionals. The meaningfulness of one's contribution to progress can certainly sway opinion, but the likelihood that this mother's contribution could justify the years of life she lost and the innumerable other opportunities she might have had to do good during those years is debatable at best. Here, I would argue that Beecher revealed just how seductive the promise of the theoretically, though highly improbable, possible is for parents and children in crisis.

Concluding Remarks

The early research codes focused primarily on non-beneficial research; but potentially beneficial research, as in the case of early phase studies, is not much different because these studies may pose far more risk than a patently non-beneficial project or one with only minor benefit. Rehashing the questionable history of earlier research practices may appear unrelated to our objectives, but there are three important takeaway points here that will feature in subsequent chapters. First, Nuremberg reminds us how important consent is and how vulnerable children are because they cannot give legally effective consent. They are of necessity largely at the mercy of

others. This is not always negative, but it does make a person more vulnerable to the opinions and needs of others even when it is to one's own detriment. Phase 1 trials are commonly seen as innovative therapy, and adults are then allowed to foist their own values about the need for research and the benefits of it onto children. This is not necessarily intentional but none the less real. Especially when children are dying, it can be tempting to do anything in order to make their death have meaning for those left behind, either through helping parents feel they have done everything possible or attempting to create a legacy of service and sacrifice for the child. It is, however, presumptive to assume that these efforts are inherently valuable to children.

Secondly, the social precept that participation in research is at some level a moral duty, as implied in the Declaration of Helsinki, can easily become a coercive influence. Social pressure can become nearly as effective a mechanism for encouraging research as material benefits. When these duties are imputed to children, adults often assume moral capacities and requirements that may not be present. Participation in a shared morality requires the intellectual, social, and moral capacities for engagement, and children may not have all of the relevant capacities. In the case of the seriously ill or dying child, these capacities may never fully develop. Not to mention, we only allow children to make certain sacrifices. How can we justify allowing dying children to make a large sacrifice when they may never come to know the moral good of such a sacrifice?

Lastly, the events at Willowbrook call into question how physicians and parents make risk-benefit determinations. Krugman and his colleagues made these determinations based on the horrible conditions in the institution, and parents were forced to weigh either the prospect of admission or their children continuing without treatment. A parent of a seriously ill child makes similar tradeoffs today. The question of how much risk is too much when it may mean access to a miraculous outcome has yet to be satisfactorily answered. But, it is a mistake to think that just

because children are hurting or vulnerable they can automatically be placed at great risk for minimal benefit. Even when we have the best intentions, we must be honest about how much benefit they can really hope to gain.

Research ethics' early history is not concerned solely with past problems but with present questions, and we will return to these ideas in later chapters. Medicine as a discipline is always advancing. Though early phase trials today may look different to us than historical innovations, they represent the new frontier with all of its potential successes and pitfalls. Helsinki first opened the door to research with those patients unable to give consent, and physicians began to conduct many primitive projects. Willowbrook is one illustrative example. But, the events at Willowbrook showed a need to more definitively articulate how and why children should be included in research. In the ensuing debate, Paul Ramsey and Richard McCormick rose to the challenge.

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Chapter Two

Regulations Concerning Children in Research

By the late 1960s and 1970s in the aftermath of Beecher's revelations, many questions were being raised about the protection of research subjects and whether the inclusion of children in research was justifiable. The U.S. government convened the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 to consider comprehensive guidelines for the conduct of federally-supported research. The National Commission was specifically charged with insuring protection for vulnerable individuals, including children, institutionalized developmentally disabled persons, and prisoners (Jonsen, 2003, p. 100). The Commission issued a report on children in research in 1977 followed by the now famous Belmont Report in 1978 (Jonsen, 2003, p. 102). When considering the ethics of research with children, the Commission was profoundly impacted by the work of two theologians, Paul Ramsey and Richard McCormick, who had both publically taken up the question of whether children could be included in non-therapeutic research. The National Commission invited both men to speak and debate the issue (Jonsen, 2003, p. 155). The outcome of this debate shaped the Commission's recommendations and the ensuing federal regulations.

Ramsey vs. McCormick

Paul Ramsey, a Princeton University theologian, was the first to take center stage in the debate. In his 1970 book *The Patient as Person*, Ramsey insisted that children should not be included in non-beneficial research because to do so was to treat children as small adults. To make sense of Ramsey's argument, we need to understand Ramsey's general perspective on the

relationship between physician and patient along with his conceptualization of research as a joint venture. Coming from a Protestant background emphasizing covenant theology, Paul Ramsey unapologetically focused on a covenantal relationship between physicians and patients rather than a contractual one. Whereas contractual medicine simply requires a legal agreement (i.e. contract) between two parties specifying what each will do, a covenant commits the physician to seeking the patient's good- to becoming a fiduciary for the patient's greater interests. Patients do sometimes consent to (i.e. contract for) certain medical services, but they do so in the larger context of a covenant where the physician promises to be primarily concerned with their welfare and interests. This covenantal relationship allows patients to fully trust their physician's intentions and motivations. Providing medical care requires far more than simply providing a list of agreed upon services.

Ramey argued that medical ethics properly understood was not a utilitarian "greatest good for the greatest number" ethics, and physicians could not justify the sacrifice of an individual patient's interests for medical progress. Rather, medical ethics has a deontological dimension manifest as a "chief canon of loyalty" between patient and physician-investigator (Ramsey, 2002, p. 2). Here, Ramsey does not draw sharp distinctions between the duties of physicians and of physician-investigators. If one presents oneself as a physician, patients should be able to expect a certain loyalty. That is, physicians do not cede their underlying responsibilities to patients when they engage in medical research. While I believe Ramsey would apply this uniformly to physicians, he would likely be even more concerned when physicians recruit their own patients or are assuming responsibilities for clinical and research-related care simultaneously. Here, Ramsey recognizes the implicit power of the white coat. Patients should

be able to trust it as symbolic of a covenant to promote their good, and participating in research may not always promote this good.

For Ramsey, the informed consent process then is not a mere exchange of information or the autonomous choice of a patient to engage in a certain course of action for their own good or humanity's greater good. Informed consent cements a relationship of fidelity between physician-investigator and research subject in which both become joint participants in a research enterprise (Ramsey, 2002, p. 6). Both parties know what is at stake when their relationship changes, and the patient must decide if participation will further his aggregate interest. Conducting research without patient understanding would violate the covenant the physician makes to rigorously promote the individual's interests above his own or anyone else's. This covenant cannot be defined by a set of rules; rather, it requires a purity of motivation or intent. The physician can only continue to claim that his motivation is to promote individual interests in research if the patient himself determines that such a project is actually part of his aggregate interests. Ramsey particularly warned against the future wearing down of the consent requirement through indirect means that would render consent a powerless guideline. The medical community must also always be careful not to undermine consent with appeals to future benefits (Ramsey, 2002, p. 11).

Since informed consent in Ramsey's view is required, those who cannot provide informed consent and thereby become joint venturers in an investigation, including children and incompetent persons, are not eligible to participate in non-beneficial research. Becoming a knowledgeable joint venturer is to freely embark on a research protocol as a partner with the physician. The competent patient can decide to cede some of his interests for the sake of other values or in pursuit of his greater interests, but the incompetent child cannot make such a

decision. To include children in these cases is to treat them as adults who are capable of becoming joint participants in such an investigation (Ramsey, 2002, p. 14). Parental consent is an insufficient mechanism for children's participation in non-beneficial research because parents also have a covenant with their child that precludes them from exposing children to risk with no prospect of benefit. Therefore, children may only be included in research when their inclusion is likely to further their own recovery (Ramsey, 2002, p. 12).

Ramsey admits that what constitutes a sufficient benefit to the child is often difficult to define if we consider any possible benefit that may occur, and he does not provide guidelines on what constitutes an acceptable likelihood of furthering a child's recovery. But, in cases where research procedures present no prospect of direct benefit, children should not be included. As Ramsey explained, "This situation [where giving an experimental drug is the only reasonable treatment] also justifies a parent or guardian in consenting for a child, since we are supposing the hazard of the proposed treatment to be less or no greater than the hazard of the disease itself when treated by the established procedures" (Ramsey, 2002, p. 15). Here, Ramsey (2002) leaves open the possibility of including children in vaccine research in cases of epidemics or other crisis situations (Rasey, 2002, pp. 15-16).

Although I believe this statement may leave open the possibility of including children in early phase research, we do have to consider whether there really is a likelihood of benefit, especially if children must give up significant experiences or spend time away from home when they are near death. In a vaccine situation during an epidemic, researchers would give an antigen in the hopes of actually inducing immunity. In most cases, the worst thing that could happen would be contracting the infectious disease. The vaccine would not necessarily make the disease more burdensome once a child had contracted it, and a successful outcome would be in fact a

clinically significant immunity. At first, a similar argument appears possible for phase 1 trials. The worst thing that can happen to a dying child is death; therefore, whether he experiences toxicity from an experimental drug without personal benefit or dies from the normal course of his disease he will still die. Yet, phase 1 trials are not much concerned with clinical outcomes. They are concerned with dosing and toxicity. A phase 1 trial can be successful even when no child clinically benefits so long as dosing ranges are determined and toxicity levels noted. In my opinion, phase 1 trials would have to be restructured to provide maximum clinical benefit, rendering some options like randomization, subclinical starting doses, etc. out of the question if we wish to rely on Ramsey's appeal to research in emergency situations or epidemics to justify phase 1 endeavors.

If taken seriously, Ramsey's arguments prohibit some potentially very useful and low-risk research with children (i.e. surveys, optional diagnostic studies not used for clinical purposes, etc.). Many low-risk research projects that do not provide a discernible direct benefit would be forbidden. For instance, educational researchers might not be permitted to survey students about their mental health unless that information was directly used to benefit them. The public health or collective educational benefits from characterizing the prevalence of mental health symptoms would not be enough to justify the lack of direct benefit, even though children would not likely be harmed by taking a survey. While risky, potentially therapeutic research might be justifiable, a much safer research project might be ruled out even though it poses less risk to children's overall interests.

In response, Richard McCormick offered a rebuttal argument in favor of including children in some types of non-beneficial research. Appealing to traditional Catholic moral theology, McCormick contended that parental consent was actually a form of vicarious consent

based on what a child would and ought to wish if he were capable of making decisions himself (McCormick, 1974, p. 9). For McCormick, determining what a person ought to wish could be deduced by examining what goods man could seek consistent with his own flourishing. For example, a parent was right to consent to medical therapy for a child precisely because life and health are goods a child ought to wish for himself (McCormick, 1974, p. 12). That is, they are objective goods common to all persons. As a social being, the individual also should generally seek the good of others. Participation in non-therapeutic research represents a sharing of the benefits and burdens of medical advancement and is both an individual and collective good.

McCormick did establish two important limits on when any person should participate in research. First, he contended that whether or not it is good for a certain individual to participate in research depends on that individual's particular circumstances, personality, future plans, etc. Secondly, he reiterated the importance of voluntary consent. The good of shared participation can only be realized when individuals (or presumably their parents and guardians) freely consent to the research project (McCormick, 1974, p. 13). McCormick (1974) then proceeds to argue in favor of non-beneficial research that requires the use of children but does not cause significant harm or discomfort to the child patient (p. 14). Here, he uses an appeal to what is now termed a risk-benefit ratio. If the risk-benefit ratio, which includes both the benefits to society and to the individual, is acceptable and risks minimized, children, as members of the human community, ought to want to help others; and participation in non-therapeutic research is acceptable. For McCormick, such participation was not heroic and came simply from recognizing that people should seek the good of others.

McCormick believes that Ramsey gets the ethics of proxy consent wrong specifically because he fails to grasp why proxy consent is valid in the therapeutic setting- because a child

would and ought to act for the sake of her own health. By extension, the child ought to care about the health of others insofar as she is a member of the human community. Interestingly, McCormick also provides for times when parents may refuse treatment on the basis of what a child ought to want. As an example, he makes a distinction between ordinary and extraordinary clinical care. He explains:

> Once it is accepted that one need not per se use extraordinary measures to preserve life and that this is true also of infants, it remains only to ask who is to make this decision for the child…However, just as parental consent to therapy is not arbitrary and capricious but represents a reasonable presumption of the infant's wishes because he ought to want to preserve his life, so denial of consent must be traced to what the child would not want because it is beyond what he ought to want. (McCormick, 1974, pp. 18-19)

Paul Ramsey replied to McCormick's novel argument in favor of the legitimacy of parental consent on the basis of what children ought to wish in a 1976 article where he re-stated his opposition to such an analysis. Ramsey admitted that some necessary non-beneficial research might need to be conducted with children, and researchers must do the research while knowingly violating the maxim not to use children. Here, Ramsey strikes a compromise by acknowledging that there may be some cases where individual interests have to be sacrificed in the name of the greater good, but the tradeoff should not be obscured under the guise of children's moral duties. Researchers should not justify the use of children on the basis of what the children themselves should want. Rather, researchers should recognize that there are moral evils arising from failing to do vital research in the pursuit of medical progress as well as evils from using children who cannot consent. Researchers must choose the least evil option while still recognizing that they are fundamentally doing some amount of moral evil.

Ramsey contended that McCormick's position had a moralistic quality and would weaken protections for children in research by rendering their participation an expectation instead of a moral exception. By jettisoning the ethical tension inherent in performing research that is morally praiseworthy on children who cannot consent to be used for such a purpose, McCormick achieved a satisfactory resolution to the moral problem but did so with a flawed understanding of parental responsibility. Ramsey contends that McCormick treats children as merely small adults who would and ought to naturally be inclined toward those things that adults value.

On the other hand, Ramsey argues for the need to differentiate between what the good human nature inclines toward generally is and the specific goods of childhood. Children are at least initially inclined only to seek their own well-being. The good of sacrifice is a concept adults recognize to varying degrees- not one innate to children. Parents are to preserve the good of childhood itself, not just some eventual good the child ought to wish for when an adult. For Ramsey, *would* and *should* are not separable for children.

> To stop at the implied 'would consent if he could' need not be based on voluntarism in ethics. It is sufficient to say that in a child the *would* and the *should* are identical; the imperatives of parental care are the same. It is only later in human development, when consent and other moral choices may actually diverge from the basic human inclinations, that a time comes when the *should* can properly be set against the *would*. (Ramsey, 1976, p. 23)

This statement lends itself to empirical verification in some respects. If children would consent to something, then perhaps, they should consent to it generally. However, I argue that

Ramsey would be leery of children engaging in activities that are not in accord with their immediate interests. Children could very well be socially pressured to prematurely separate the *would* and the *should* due to adult influence. The difficulty with his position here is that children do grow up, so the exact time when it becomes appropriate for children to sacrifice their immediate interests for their own deeply held values is uncertain. A teenager might make some sacrifices very much of his own accord. However, the larger significance of Ramsey's point stands. A young child would not generally sacrifice or suffer for someone else, and the expectation that suffering for another is sometimes necessary requires a well-developed set of moral principles associated more with maturity than youth.

To ask what a child ought to wish beyond an unimpaired life in the future is to make the child merely a small adult and to impose adult expectations and values on him. Furthermore, there is no reason to assume that allowing such vicarious consent for children cannot be extended to the incompetent, the incapacitated, the vulnerable, and those who may not volunteer to participate of their own accord. The argument that non-consenting individuals should want to participate in at least non-risky research is a type of moral accordion likely to expand or contract based on society's current research-related needs (Ramsey, 1976, p. 26-27). I argue that the recognition of non-beneficial research with children as the least evil option rather than a positive good or fulfilment of a moral duty would give investigators more pause before conducting research. It would also empower parents to make a decision based on the anticipated burdens rather than based on the idea that their children should want to participate in research. Instead of asking the question, "Why would a child not want to help others?," we would ask, "What makes this project so particularly innocuous that it does not unduly compromise children's natural self-interest?".

McCormick's (1976) final reply to Ramsey focused on rebutting assertions that his position imputed moral obligations to children or could become a moral accordion based on the need for research. First, McCormick contended that his use of the word *ought* did not imply children having actual moral responsibilities. But, children are social creatures who share in society's burdens and benefits. The goal is not to introduce the child to the adult world but to introduce her to the social world of which she is already a member (McCormick, 1976, p. 42). For McCormick, Ramsey goes wrong when he conceives of individual rights without regard for the rights of others inhabiting the same social sphere. No individual is responsible solely for himself, and children may benefit from the standpoint of their moral development when engaged in non-therapeutic, but minimally risky, research. Regarding Ramsey's second point of concern, McCormick explains that while the definition of what constitutes minimal risk must be flexible children should not be used in research when they are able to consent or assent but choose not to do so. Although children cannot give the same kind of informed consent given by a parent, they can certainly voice agreement or disagreement in many cases. The parent is also responsible for deciding if the child can benefit morally and then supervising the research experience. The research community may only propose projects consistent with the possibility of moral development (McCormick, 1976, p. 45). Thus, McCormick (1976) proposed the following guidelines for when research would be permissible:

- The experimental protocol must be subjected to careful institutional peer review.
- The experiment would provide significant and essential new knowledge.
- The knowledge to be gained by the experiment can be obtained only by experimentation involving children.

- The experiment must involve no greater risk or discomfort than would be encountered by the child in his family life.
- Where possible, the same or a similar experiment must have been performed on adult subjects and been found to be without risk.
- Informed parental consent is mandatory. Parents must be involved as experimental subjects with their children where possible. Parental supervision would be mandatory where this was not possible.
- The consent of the child subject must be obtained by a member of the research team and by an independent subject-representative.
- The research must be reviewed by an ethical review board and reviewed and supervised by an institutional protection committee. (Children in this age range must be included as members of the latter for review and supervision of experiments in this category.) (p. 45)

There are four important contemporary points to consider when thinking about the Ramsey-McCormick debate. First, it is tempting I think to characterize Ramsey as anti-research and McCormick as pro-research, but I believe these distinctions are oversimplified and do not capture the essence of the disagreement between the two men. Critics see Ramsey as prohibiting a large amount of research or as prohibiting risky research with children when in fact he does neither. Ramsey actually provides great latitude in interpreting what constitutes a reasonable benefit to the child, and he would likely support some very risky research with a loosely defined prospect of direct benefit. After all, Ramsey never sets a particular bar for the amount of direct benefit a project must offer, so he continues to provide latitude for projects with varying

probabilities of benefit. Ramsey never even defines what constitutes a reasonable therapeutic benefit, leaving room for medical experts to make their own judgments.

At the same time, Ramsey argues that researchers may sometimes have to violate the maxim not to use children in non-therapeutic research in order to conduct morally obligatory projects. He leaves us with a conundrum here where researchers would have to admit violating the rights of individual children for the sake of the greater good. Many people feel they must engage in certain necessary courses of action for the greater good, and Ramsey would not place punitive blame on these individuals. Rather, he merely insists that they not be allowed to proceed and deceive themselves about their actions. The price of moral courage can be high, and Ramsey is insisting that the price be paid. There is a difference between prohibiting conduct and requiring the acknowledgment that even practically obligatory conduct can be morally problematic. This acknowledgment can drive a never-ending quest to better research practices and improve research design.

Secondly, Ramsey's continuing contribution to current debates is his focus on the covenant between physician and patient. Ramsey correctly captures the ideal relationship between physicians and patients as a "covenant of loyalty." The rapidly changing medical landscape sometimes makes previously established relational patterns appear stale or inadequate, but patients continue to see physicians in many respects as they always have. Ask anyone on the street why they trust their personal physicians or emergency medical professionals and they will likely refer to some combination of professionals having taken an oath, the medical profession being devoted to patient welfare, or the profession's long-standing self-policing. A December 2015 Gallup poll revealed that 67% of respondents rated medical doctors as being highly honest and possessing high ethical standards.

Physicians are given power and are therefore expected to wield such power judiciously. When a person enters a physician's office, she does not think of her doctor's competing obligations. She sees the physician as having made a commitment to her welfare. If she comes to believe the physician has other priorities, she will, if able, likely seek care from another source. One could argue that I am merely confusing the roles of physician and researcher (as so many do), but physicians do not cease to be physicians when they put on the researcher's hat. The patient still knows she is seeing a doctor. Research often takes place in a clinical medical environment. Sometimes, the researchers are also the foremost experts on a disease, and the patient has little choice but to see a particular doctor. In pediatric cancer, the treating physicians are often the ones offering trial participation in the first place. Ignoring the special obligations physicians have to their patients makes light of the profession's unique role and normative power. Patient care is not merely one of many equally important activities. It is the hallmark of medicine.

Third, McCormick's reliance on defining what people ought to wish and the amorphous definition of what constitutes minimal risk is prone to error, especially when he includes children. Many adults disagree on just what their obligations to society are, and it would be presumptuous to argue out of hand that such disagreements are rooted primarily in selfishness or ignorance. For instance, consider the example of physicians' personal preferences when facing terminal illness. In a 2014 survey, Chinn et al. found that approximately 65% of physicians who care for cancer patients would themselves choose hospice in a similar situation. The survey juxtaposed hospice care and continued aggressive treatment, so I would surmise that this means physicians would also not pursue aggressive experimental protocols. But, would we say they had not fulfilled their moral obligations to society because they did not subject themselves to medical

research? I doubt it. And, what of the child who cannot yet dissent or assent? When reasonable adults cannot agree, presuming the wishes of the child is very difficult.

Fourth, it is unclear that a child can morally understand or learn from research participation in the same way that a competent adult can. McCormick does insist that children who can assent should be given the opportunity to do so and should not be forced to participate in research, but this does not help for very young children or children who are incapacitated from an illness or injury. His caution also does not prohibit parents from convincing their child to participate by appealing to moral guidelines and responsibilities. Yet, part of the moral benefit of research participation comes from understanding that one is making a sacrifice for the greater good and of truly appreciating the potential gravity of that sacrifice. Some children may be able to understand complex moral concepts, but some children also clearly cannot understand these ideas. Childhood is a special carefree time partly because children lack a sense of substantial obligations or an understanding that bad things frequently happen. While children should be taught to respect the rights of others, it is debatable whether people can make demands on others when those demands place others at risk, let alone when those others are children. Children gradually mature and respond to moral examples, but I would argue against moral coercion as a helpful instrument for shaping character when it comes to positive duties. It is one thing to punish a child for violating certain boundaries, but positive duties are a slightly different matter. One must be shown empathy in order to eventually show empathy himself. Developing a willingness to take on positive duties often comes from the examples of adults and the sense that adults have made sacrifices for your own sake. Asking for significant sacrifices before a child is even capable of articulating those sacrifices is rather extreme. Empathizing with the child means not placing burdens on him that he is not developmentally able to accept or appreciate.

McCormick's argument that children ought to wish to help others is difficult to defend in this context. Parental consent is valid for treatment that customarily offers direct benefit. But, can children be categorically expected to want to take on serious risks for unlikely benefit? I am not so sure. However, an example from outside medicine may be helpful here in illustrating how we routinely view children when it comes to making serious sacrifices. No one would argue against the idea that firefighters make a sacrifice for the greater good. They run into burning buildings in order to save lives, risking their own in the process. Many fire departments are staffed by volunteers, and some have volunteer service programs for teens. But, teens are not allowed to actually fight fires until they are somewhere between ages 18-21. A high school student may desperately want to make this sort of sacrifice, but we do not permit it until he understands what he may be giving up. If children are terminally ill and forced to make serious tradeoffs, surely we should not be so quick to surmise that they will want to make large sacrifices, especially when we do not allow them to do so in other, less coercive contexts.

The Ramsey-McCormick Debate and Pediatric Phase 1 Trials

Although Ramsey and McCormick were only concerned with patently non-therapeutic research, their views do have relevance to questions about early phase research. First and foremost, I believe both would insist on a rigorous interpretation of what constitutes a direct benefit. The off chance of something happening may not be enough for either one to call phase 1 trials potentially beneficial. We will discuss some probabilities about the potential benefit of phase 1 trials later. But, phase 1 trials may be more akin to non-therapeutic rather than therapeutic research.

If Ramsey and McCormick were to consider phase 1 trials as non-beneficial research, McCormick might still approve on the grounds that a child has little to lose and physicians can minimize symptoms of toxicity while producing an aggregate benefit; but, I doubt very much Ramsey would approve. Ramsey was concerned about minor inconveniences, so he would be even more concerned about a situation where benefits are at most unintended and risks are serious. Yet, Ramsey does offer us a potential solution here that is, in my opinion, superior to the argument that children should want to participate in research.

Phase 1 research may be necessary and even obligatory for researchers in order to advance medicine, but its moral justification cannot hinge on what children ought to wish as individuals or as members of the social world. Researchers would use children despite the fact that they ought not to be used in the service of collective objectives, and parents would need to view their children's participation as a sacrifice for the greater good- not an innovative treatment option.

Importantly, physicians could not claim to be fulfilling their covenant with the pediatric patient. They could not simultaneously claim to be both physicians and researchers, though throughout the course of their careers they might engage in both clinical work and research. I argue that it is necessary in any particular case to either have responsibility for performing research or for providing patient care- a difficult, but not tragic outcome. This change in identity would require a clear separation between researcher and attending physician, and the attending physician would need to have authority to override the researcher based on the child's needs. The researcher would release himself from his general obligations as a physician and thereby be bound to the researcher's code of conduct instead of the covenant between child and physician. A researcher's conduct must necessarily be judged in some ways differently than a physician's

conduct because of the nature of the work in which she is engaged. In the final chapter, I will discuss how this separation might play out in practice.

Federal Regulations

The National Commission largely adopted McCormick's views when issuing the Belmont Report and making contributions to the national regulations. The Belmont Report attempts to precisely distinguish research and practice and provides three ethical precepts for the conduct of all research. While the goal of practice is to benefit individuals, the goal of research is to produce generalizable knowledge. Belmont's well-known precepts include autonomy, beneficence, and justice. In pediatric phase 1 trials, beneficence is the source of most ethical qualms, as individual children are unlikely to benefit. At the same time, children as a group benefit from such research, leading to possible satisfaction of the precept despite individual risk (Haylett, 2009). Regarding autonomy, the National Commission attempted to strike a middle position between child empowerment on the one hand and protection on the other by emphasizing parental consent, child assent when appropriate, and specific protections for the incarcerated and wards of the state (Carroll and Gutmann, 2011).

Today, the *Code of Federal Regulations* (2009), promulgated by the Department of Health and Human Services and sometimes referred to in shorthand as 45 CFR 46 or the Common Rule, continues to guide research with children. For our purposes, Subpart A and Subpart D are the applicable regulations. Regulations in Subpart A apply to all federally funded research. Subpart A specifies such things as IRB membership requirements and duties, definitions, criteria for project review, record-keeping procedures, and general standards for research conduct (Institute of Medicine, 2004, pp. 95-100). All researchers must comply with

Subpart A, whether they work with competent adults or another population. But, children are given special protection. Subpart D specifically outlines the categories of permissible research with children and sets special standards above and beyond the requirements for research with consenting adults. Children are by default considered to be a vulnerable population under the Common Rule.

There is a preliminary point to consider before diving into the four categories of federally permissible research with children. The approval of any research project always requires the IRB, along with the investigator, to make a determination of the risk-benefit ratio. The benefits weighed include both those to the individual participants and more general benefits to society generated from the research project. The risks considered are subject-focused and include harms or inconveniences participants may face when enrolled in the research as well as any risks to others from the subject's involvement in research. Benefits and risks "have the dimensions of probability, magnitude, and duration" (Institute of Medicine, 2004, p.115). A project approved based on the likelihood of significant societal benefits may very well place participants at individual risk with a low or no prospect of concomitant benefit. Thus, the risk-benefit determination process used in early phase clinical trials does not only consider whether individual benefits and risks are favorable but whether individual and collective benefits outweigh risks. A trial can proceed even if the balance of individual and social benefits tips in the favor of collective future benefits.

To be sure, no one wishes to place subjects at undue risk, and there is a general duty to minimize risks as much as possible. IRBs are allowed to consider whether alternatives have been exhausted and whether an experimental intervention poses increased risk compared to the natural outcome of the disease. But, it is an error to believe that the very fact a trial is allowed to proceed

implies some sort of likely individual benefit. Likewise, it is intellectually dishonest for trials to be advertised as though they are being conducted primarily for an individual's benefit. There are some specific issues in determining acceptable risk-benefit ratios in research with children, but this general point helps to focus the next conversation.

The Permissible Categories of Research

The four kinds of permissible research with children are research that presents no greater than minimal risk, research that involves greater than minimal risk but also presents a prospect of direct benefit, research involving greater than minimal risk and no prospect of direct benefit but which is likely to yield generalizable knowledge about a subject's disorder or condition, and research not otherwise able to be approved but that is likely to yield vitally significant information about a disease (Institute of Medicine, 2004, pp. 102-03). All research requires parental consent, although standards for when child assent is also required vary based on circumstances and institutional practice. Theoretically, child assent provides children with an opportunity to express their willingness to be involved with a project according to their developmental capacities and acknowledges a child's growing, though not fully mature, ability to act autonomously.

In the first category, an IRB can approve research that does not involve greater than minimal risk so long as provisions for parental consent and/or child assent are sufficient (Department of Health and Human Services, 2009, §46.404). The definition of minimal risk is somewhat open to interpretation but is generally taken to mean those that pose no more risk than a child encounters in daily life or when undergoing routine psychological or physical examinations (Institute of Medicine, 2004, p. 117). Importantly, the minimal risk criterion

defines everyday life as that of so-called "normal" children. A child's medical situation cannot be used to judge what risks he might face in everyday life and thereby allow higher risk projects to be categorized as minimal (Institute of Medicine, 2004, p.121-22). Potential projects that fall into this first category include routine educational tests or surveys and everyday medical procedures like blood draws or physical exams. These cases fit nicely into Richard McCormick's notion that people should want to contribute to the good of society, especially when inconveniences are only minor. A child might develop morally by contributing to the good of others. Since humans are social creatures and members of a community by default, participation in these types of projects can reasonably be construed as aligning with individual and collective interests. For Ramsey, children should not be used in non-beneficial research, but this would be a case where researchers might not have to feel very guilty about sinning.

In the second category, research that presents more than minimal risk to children can be approved if it provides a prospect of direct benefit. To be approved the following conditions must be met:

> (a) The risk is justified by the anticipated benefit to the subjects;
>
> (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
>
> (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408. (Department of Health and Human Services, 2009, §46.405)

This category is the one under which IRBs routinely review phase 1 trials. Importantly, the concept of direct benefit means a tangible positive benefit to the individual participant

(Institute of Medicine, 2004, p. 132). Indirect benefits (i.e. the benefits of moral growth, inclusion benefits, compensation, etc.) cannot be used as justification for exposure to significant risk. The second criterion introduces an interesting twist in the discussion by allowing the IRB to consider the risks and benefits of available alternatives. Since most phase 1 trial participants are seriously ill or nearing death, available alternatives are unlikely to offer a better risk-benefit ratio if we strictly consider length of life and the possible miracle cure. This narrow focus on length of life renders quality of life a secondary player in medical judgments, and I will later argue that minimizing the importance of quality of life is near-sighted. A commonly employed argument in favor of phase 1 trials then becomes something like, "Although the purpose of phase 1 trials is not therapeutic and the risks more than routine, they represent a superior option compared to giving up." The alternative of "giving up" on curative therapy allows children to be placed at unknown or high risk even when the trial's likelihood of making a substantial difference is low. Here, I think McCormick and Ramsey would agree that there should be a real chance of direct benefit, but it is unclear what this requirement would look like in actuality. However, McCormick might argue that dying children should want to help others if burdens are minimized. Ramsey would probably come down on the side of caution and at most might allow research to proceed with the understanding that extraordinary protective measures be taken in the face of such grave sin. As an example, Ramsey might require outside physicians to monitor children or might require that the bar for allowable toxicity before a child is taken off protocol to be greatly reduced.

The third category of approvable research involves projects posing greater than minimal risk with no prospect of direct benefit but likely to yield generalizable knowledge about the

participants' disease or medical diagnosis (Department of Health and Human Services, 2009, §46.406). The following criteria must be met:

> (a) The risk represents a minor increase over minimal risk;
>
> (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
>
> (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
>
> (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408. (§46.406)

Interestingly, phase 1 trials are not generally reviewed under this category, likely because, as Lainie Friedman-Ross (2006, Loc 1661/4226) notes, a trial where the goal is to induce toxicity likely poses more than minimal risk.

Finally, research that is otherwise not approvable but presents an opportunity to learn about serious pediatric conditions may be reviewed and possibly approved at the federal level. In theory, projects approved under this category can have any level of risk. Hence, there is a need for federal review. The Department of Health and Human Services (2009) may approve this type of research only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408. (§46.407)

Inherent Conflicts in Federal Regulations

To my mind, there are two primary problems inherent in the federal regulations governing the conduct of research with children when thinking about phase 1 trials. First and foremost, there is no sufficient benchmark provided for judging what constitutes a prospect of direct benefit, leaving investigators and IRBs to rely on logic or emotion to make this determination in difficult cases. Investigators are encouraged to consider the magnitude and likelihood of given benefits and risks but are never told what an acceptable probability of benefit is. It seems to me that magnitude and likelihood matter, but it is difficult to argue against

magnitude in a situation where everyone is hoping for the miracle. While this lack is likely an attempt not to be too dogmatic about how individuals may weigh risks and benefits in difficult circumstances, it also leaves protocol reviewers in a bind. Logically, a phase I trial is not usually designed to sufficiently treat a condition, so it would seem there is little prospect of direct benefit. At the same time, one also cannot logically rule out the possibility of unintended benefit. Emotionally, it is only human to think in terms of the potential miracle for the seriously ill child rather than the likely continued suffering and death of that child. The miracle is always possible, though not realistic. Providing that chance feels like a moral necessity; and without any guidelines to the contrary, it is easy to assume patient consent provides justification when the likelihood of benefit is small but not zero. A lack of alternatives, zeal for knowledge, and family autonomy can then become sufficient to legally justify phase 1 trials (Petrini, 2013). In the next chapters, we will think about whether phase 1 trials are in fact good for families.

The second problem stems from the first problem. If we cannot set a bar for the reasonableness or likelihood of a benefit, then some miniscule chance of a large-magnitude direct benefit can be used to justify nearly any level of risk. For instance, if we are allowed to consider a very good but exceptionally unlikely outcome, including remission or prolonged survival, then nearly any risk, including a small risk of hastened death or increased pain, seems reasonable. Yet, this means that many children will be exposed to significant burdens without much or even any hope of benefit at a time when they are likely already suffering. Especially when trial participation may require families to travel far from home, children to remain in hospitals, and the forfeiture of opportunities to engage in fun activities, why should we allow the hope for some unlikely miracle to justify these losses? Trying to presume what the child should

want, a la McCormick, is almost impossible when adults often disagree over these sorts of decisions.

How Much Benefit is Likely from Phase 1 Trials?

Just how likely is a child to personally benefit from a phase 1 trial? Answering that question is more difficult than it appears due to the variety of trial designs used and the heterogeneity of the pediatric cancer population, but some meta-analyses do exist. To start, it is important to consider how few investigational drugs make it through clinical trials and are approved for use- that is, how many are truly clinical game-changers. From 2003 to 2011, the likelihood of an investigational agent progressing from a phase 1 trial to FDA approval was 10.4% for any indication (Hey et al., 2014). So, it is reasonable to assume that in the grand scheme of things an individual investigational drug is unlikely to actually be game-changing. Though drugs being tested in children have often been previously given to adults, there are cancers unique to children. Additionally, some children are included in phase 1 trials designed for adults.

Two recent studies tracking the outcomes of children involved in phase 1 and phase 2 research reveal equally low probabilities of clinically significant improvement. A 2008 meta-analysis by Kim et al. demonstrated that children with refractory solid tumors enrolled in one of sixteen phase 1 trials at the National Cancer Institute between 1992 and 2005 experienced a complete or partial tumor response in 4% of all cases and had stable disease in 17% of cases. The clinical significance of tumor response varies. Seventeen percent of participants experienced a drug-related toxicity, and 5% withdrew from the trial due to toxicity. Most patients were on more than one therapeutic medication during the trial. Only one patient death attributable to an

investigational agent was reported, indicating a low risk of death from experimental agents themselves. Median survival was five months (Kim et al., 2008).

A second meta-analysis of pediatric phase 1 and phase 2 participants at London's Royal Marsden Hospital concluded that most trial participants (76%) discontinued participation due to disease progression and only remained on protocol an average of 1.3 months in phase 1 trials and 3.3 months in phase 2 trials. Though toxicity was rare in this study (13%), little concomitant benefit was apparent. In the final analysis, the authors admit that families are willing to go to great lengths to access trials even though their children have poor prognoses with little likelihood of significant benefit. Yet, there is a need to continue phase 1 trials for the sake of future patients (Morgenstern et al., 2014). A third study assessed the outcomes of forty children participating in adult phase 1 trials at M.D. Anderson Cancer Center. Median overall survival was 8.5 months, while progression free survival was 2.8 months. Multiple subjects were on more than one phase 1 trial protocol (Corrales-Medina, 2014). Taken together, the evidence of significant benefit is low in these studies. Arguments in favor of phase 1 trials on the basis of individual benefit are shaky at best, and children on phase 1 trials should be given hospice care on the basis that they are likely to live less than one year.

Review Categories and Phase 1 Research

One way of addressing the ethical issues inherent in phase 1 research is to reconsider under which category these projects should be reviewed. It is fairly intuitive that these projects present more than minimal risk, but they could be reviewed under §46.406. If reviewed under this category, phase 1 trial protocols would be considered at the federal level. However, I find little reason to believe that review at the federal level would lead to vigorous ethical analysis. A

review at the federal level is just as likely as a review at the local level to result in a determination of possible direct benefit on the basis of a hoped for, but improbable, chance.

Still, there may be a way to review phase 1 trials under some new category. Lainie Ross (2006) has suggested the possibility that phase 1 trials could be reviewed as providing the possibility for "secondary direct benefit." This category would allow reviewers to adequately capture investigators' intent to study safety rather than efficacy while acknowledging that some unintended benefit may occasionally result. Ross (2006) also suggests that the child's dissent would be dispositive, as phase 1 trials would not be considered traditionally therapeutic in nature. I believe that Ross makes an important move here, but I wish to push the argument further. It seems to me that acknowledging only a "secondary direct benefit" still requires us to explain what allows physicians to morally offer probably non-beneficial research to children, when parents can consent to such projects, and the extent to which children can have the capacity to make participation-related decisions. Furthermore, acknowledging that children are extremely ill and likely to die from their disease despite trial participation leads to a whole host of questions about whether trial design should maximize possible clinical benefit and to what extent children in clinical trials should be guaranteed or even required to participate in hospice care.

Continuing Concerns

Without a true moral framework for early phase research that is situated in the relational context of parents, children, and physicians, public debates over research ethics continue to swirl. By and large, few argue that phase 1 trials are actually not therapeutic in nature. Research advocates are promoting ever greater fusion with clinical practice. Recently, there has been a cry for regulation reform that would give investigators greater latitude in conducting research and

allow for a faster pace of scientific discovery. There are real concerns that both local IRBs and larger regulatory structures unduly burden researchers and slow progress even while there is a growing need for more research. Writing in a 2012 editorial, Simon Whitney bemoaned the restrictions placed on pediatric research by IRBs, comparing such restrictions to a python's embrace. Whitney (2012) insists that the costs of IRB regulations, including time and money, potentially biased trial participation, and lag time in the search for new therapies, are simply too high to pay in many cases. The pitting of the needs of today's patients against the needs of future patients creates an extreme incentive to allow for more flexible ethical oversight.

Additionally, there are arguments that research should become more integrated with clinical care as a matter of expediency. COG has already created such a system where research and routine practice are effectively one and the same. Now, the American Academy of Pediatrics has recently implemented collaborative improvement networks among subspecialists to test and standardize best practices in children's hospitals (Lannon and Peterson, 2013). While health care improvement is a laudable goal, initiatives like these further entwine research and standard practice with no additional scrutiny. The line becomes thinner and thinner, fueling more misconceptions about research participation's benefits and burdens.

This ever increasing fusion between practice and research has led to calls for third party payers to cover experimental therapies and to legal appeals for all patients to have access to potentially therapeutic interventions. Along with calls for financial coverage, Republican legislators introduced the Right to Try Act of 2015 over this past summer (Johnson, 2015). The Right to Try Act would prevent federal authorities from stopping the manufacture, distribution, and use of experimental drugs by terminally ill patients. Proponents argue that the law is really just an effort to allow individual patients to work with their doctors in order to preserve their

lives. The law does not require drug companies to provide medications but does allow for an effective bypass of the FDA approval mechanism. Critics worry that making drugs available before they are sufficiently tested may impede research progress and usurp FDA guidelines on expanded access for the terminally ill (Johnson, 2015).

At the same time, there is little promising evidence to suggest that Americans truly differentiate between research and practice or are willing to accept great clinical risk to participate in research. Statements made to the media routinely indicate that parents and children perceive clinical trials as synonymous with medical care. For example, a recent article in the *Lansing State Journal* described a Haslett fifth-grader's struggle with brain cancer. Will Goodale was diagnosed over the summer, and his parents hoped to enroll him in a clinical trial to offset treatment costs. Will was not eligible for the first trials the family considered and missed one study's cutoff time between diagnosis and treatment. The FDA approved a compassionate use application. Will's father did seem to understand that his son's use of other treatments would have been restricted in a clinical trial, but he mentioned nothing about risks or unknown complications. He even argued that their use of an experimental drug outside of a research protocol might be beneficial, since they could keep an eye out for a trial or treatment that might be better (Smith 2015).

It is clear that Will's family actively searched across the nation for a clinical trial, but it is unclear that they understood the distinction between clinical care and research. Will was not likely to be the primary beneficiary of clinical research, as he might have been with clinical care. Research does not mean cutting edge treatment; it means being given an unknown that could literally, at least in early phase settings, turn out to be a poison. I certainly hope they did understand; but, the fact that they would cite cost as one major contributor to their decisions is

concerning, as clinical trials come with burdens and risks as well as benefits. This is not to say that cost should never have any impact on medical care, but it is worrisome when parents with a recently diagnosed child are so eager to enroll in a clinical trial while failing to acknowledge real research-related risks.

An Alternative Voice

Despite the perceived necessity for research, there have long been philosophers who have championed a more restrained approach, and we would do well to consider these voices in the face of current questions. As an illustrative example, Hans Jonas, a German-born philosopher and Nazi escapee, argued that while there are some things society truly cannot afford, like pestilence or a death rate that exceeds the birth rate, many improvements in health are truly optional (1969, p. 229). A tolerably stable death rate from some disease is not sufficient to justify the conscription of individuals into experimental service. The human response to these deaths is understandable, but pain and grief do not always give rise to concomitant moral responsibilities. A person does not owe another living person or a future person medical progress. As Jonas explains, "Let us finally remember that it cannot be the aim of progress to abolish the lot of mortality. Of some ill or other, each of us will die. Our mortal condition is upon us with its harshness but also its wisdom…" (1969, p. 245). Indeed, a truly intolerable social condition would develop if everyone was expected to routinely sacrifice themselves for the sick and dying, and it would not be any different for children. We will consider Jonas' arguments in subsequent chapters when thinking about children's developing sense of morality and when considering hospice as standard care at the end of life.

Concluding Remarks

The question of how, or even if, current children's interests can be balanced with the needs of future children has not been conclusively answered, especially when research may involve significant risks and burdens but a miniscule chance of equally significant benefit. Throughout the early history of research ethics, the necessity of consent dominated discussions about ethical behavior. Patient or guardian consent served as justification for aggressively pushing a research-focused medical agenda. The Ramsey-McCormick debate attempted to answer why and when physicians should offer and parents could consent to research and when children ought to accept parental wishes by willingly participating in research, but questions remain. The wholescale acceptance of Richard McCormick's position has allowed medical research to be seen as a socially obligatory enterprise with little attention paid to who actually reaps the benefits of such research. In order to determine whether phase 1 research can truly be morally justified and what conditions must be satisfied, I turn next to the relational obligations shared among parents, children, and physicians. Only by analyzing what parties owe one another in their individual social context can we make generalizations about the acceptability of phase 1 trials.

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Chapter Three

Parents and Children

In the first two chapters, we have examined the history of research ethics as it specifically pertains to children as subjects. We have seen how questions about research presenting risks with few benefits have not been conclusively answered through historical precedent or federal regulation. Initially, the ethics of research revolved around the consent of the subject. The ethics of consent required that research be seen as voluntary rather than as a requirement or duty. With time, research came to be seen as a necessity with an attendant need to justify participation if individuals could not give consent for themselves. The idea of including children in research was particularly troubling, with Paul Ramsey arguing that research must benefit the individual child to be ethical and McCormick suggesting that children could be expected to participate in some projects because they should want to help others. Both assumed that potentially beneficial research was justifiable, but they gave little indication of how the term "beneficial" might be defined. Ramsey does help to the degree that he sees any justification for non-beneficial research as separable from children's interests and/or obligations. But, implicit in all of these discussions is the notion that parents should have the authority to consent, at least for some activities, on behalf of their children. The federal regulations also focus on parental consent. Thus, I turn now to focus on the parent-child relationship to see if it best justifies the enrollment of children in early phase clinical trials.

Medicine has too often undervalued the family's role and subsequently negatively disrupted families already in crisis over a loved one's illness. Near the beginning of their seminal work, *The Patient in the Family: An Ethics of Medicine and Families* (1995), the Lindemann-Nelson's give a historical treatment of the ways in which medical professionals and families

have misunderstood one another and established competing rivalries of care with both sides expecting more of each other (Loc 190/5333). Likewise, they point out that rule-based or idealized moral theories sometimes appear ridiculous when applied to families (Lindemann, Nelson and Lindemann-Nelson, 1995, Loc 1097/5333). Impartial individualism may be an ideal model in bioethics, but it is pretty useless in the lived experiences of family members who must continually balance individual and collective responsibilities. Thus, physicians and bioethicists often have trouble appreciating how and why families make the decisions they do, thereby creating frustration and conflict.

Therefore, in this chapter, I take a new approach. Since parents must make decisions about research participation no matter how we classify or regulate a given project, morality in early phase trials is perhaps best defined not only (or I daresay even primarily) through codes or legal regulations but in the context of relationships. To determine under what conditions early phase research is acceptable, we cannot ignore the relational obligations that parents and children have to one another and that physicians have to both children and families. I first consider the relationship between parent and child in order to answer questions about children's participation in early phase research.

Any systematic treatment of medical decision-making by parents, including the decision to participate in clinical research, must begin with an examination of just why we should rely on parents to make medical decisions at all. Being a parent certainly does not give a person special medical knowledge, and love for and strong attachment to a specific child may blind parents to medical realities. But, most everyone would assert that parents are best suited to make decisions for their children and need wide latitude when doing so. Some of the most powerful arguments for allowing parents to enroll their children in early phase research come from appeals to the

parent-child relationship and from the value of family autonomy. There is an obvious need to protect children if their parents fail to meet basic standards, but the autonomy and integrity of the individual family unit significantly influences good medical decision-making processes. Indeed, parental authority and values are usually seen as positive reasons for allowing parents to give proxy consent for their children in questionable circumstances. Therefore, the goal of the present chapter will be to focus on the specific goods of family life that manifest when parents exercise authority over their children. Parental decisions about aggressive medical interventions, like phase 1 trials, must then be justified by appealing to these specific goods.

The rationale for empowering families to make medical decisions has deeper roots in a philosophy of the family more generally. In order to answer the question of why and when families should make medical decisions, we need to look at what is special and valuable about families in the aggregate. Then, we can develop some realistic criteria for assessing both parental decision-making processes and outcomes and hopefully decide whether enrolling in early phase research is usually a sound parental decision likely to promote the child's and larger family's interests. Within the phase 1 context, we will need to consider whether parents are sufficiently able to protect, love, and shape their children along with whether children are able to remain in close relationship with their parents and retain their appropriate roles.

The Value of the Family

What is valuable about the family? The answers to this question along with questions about what children's and parents' interests are help us understand when to intervene, either formally or informally, on a child's behalf and when to leave well enough alone. As Brighouse and Swift identify in their 2014 book *Family Values: The Ethics of Parent-Child Relationships*,

the family presents two unique challenges in contemporary society- threats to equality and questions about the distribution of authority. We will not focus much on equality in the present discussion except to emphasize that decisions about early phase research must consider the fact that alternatives may be unequally available to children and parents and the argument that the ethical principle of justice is not enough to compel research participation. To the first point, some parents will find it harder to access hospice care for their children, or they may lack the personal, social, and economic resources to provide their part of the needed care. We will discuss the need for equity in palliative care availability in the final chapter; but, for now, it is enough to simply acknowledge that families have differing strengths, capacities, and access to medical services generally and pediatric palliative and hospice care specifically. Additionally, in light of the history of research ethics, I argue against any notion that justice should compel children to enroll in clinical trials. Children's enjoyment of collective discoveries should never result in their conscription into experimental service. To do so is, a la Ramsey, to treat children as small adults.

However, I will take up the question of authority in some detail. The question of who should exercise authority (i.e. parental discretion) comes down to the importance of family relational goods (Brighouse and Swift, 2014, p. 57). That is, children have an interest in being under the authority of one or a few individuals who know them well and are devoted to them. Adults also have an interest in exercising parental authority over their children. The family produces certain goods that would be difficult or impossible to replicate through any other means, though some of the goods of family life are not strictly about individual interests.

Children have an interest in their parent's protection and guidance through their exercise of authority. Certainly, children have some objective well-being interests, but they benefit from the great latitude parents have to provide for their interests (Brighouse and Swift, 2014, p. 60).

Part of the good of having a parent is her spontaneity in making decisions specific to an individual child. Imagine for a moment if we made a book of rules for parents with algorithms to cover every situation. Every time a child had a need, the parent would be expected to consult the book to come to a decision. This is an absurd proposition from a practicality standpoint, but it also would not be good for children. Children benefit from their parent acting in the moment to meet their needs and from learning to trust that the parent will competently respond on his own accord.

Being under the authority of a few well-known, loving individuals is a good in itself. People who know a child well and are most intimately connected to the child are best able to structure the child's daily life for his well-being. Additionally, children need the stability that such structure provides. It is much more difficult for a stranger to immediately respond to the child's individual needs and interests or to provide the continuity that a few beloved caretakers can.

From the perspective of children's interests, I argue that there are four primary things parents should do. Parents should protect their children, demonstrate their love, help children construct and refine their identity, and shape future moral character. First and foremost, parents are obligated to protect their children from significant harm and to a weaker degree to promote or protect children's health and well-being. The protector role is rooted primarily in biology. An infant is born with no capacity for self-regulation or defense and must rely on a primary caregiver for all of life's necessities. Even as she grows older, it will be a good many years before she can weigh reasons for and against decisions or deal with complex situations. Here, we can assign parental responsibility precisely because the parents are responsible for bringing a helpless human being into the world or because "causing someone to exist produces

responsibilities" (Lindemann-Nelson and Lindemann-Nelson, 1995, Loc 1450/5333). The state's regulation of parental care affirms the basic responsibility of parents to protect their children. Since phase 1 trials may present specific harms, we must consider whether we can either prevent harms or sufficiently ameliorate negative impacts.

It seems obvious to me that parents have the general responsibility to protect their children and those children's basic interests; but, if a parent only fulfilled this minimal responsibility, we might call him an adequate parent rather than a "good" parent. The good parent does more for a child than providing the minimal amount of goods and services necessary to avoid state intervention. There are higher level responsibilities in parenthood. Here, we come to the second responsibility a parent has to their children- the provision of love or, at the very least, affection. Parents usually naturally and spontaneously come to love their children. Even if parents are for some reason unable to love whole-heartedly, they can remain affectionate with their children and reflect good things about the child back to him or her. Love can be as much of a practice as it is a feeling insofar as it can be cultivated (Brighouse and Swift, 2014, p. 21). Any person can remember times where they did not feel like being loving but still acted with love. In time, reliably acting from love can change one's natural inclinations and give rise to more spontaneous emotional feelings of interpersonal love. In any case, the parent has a duty to act to meet the child's need for love even if she is not naturally motivated to spontaneously love her child (Brighouse and Swift, 2014, p. 21). It is clear that parents continue to act from love when making decisions about phase 1 trials, but they need to be empowered to prioritize their interests in a close parent-child relationship over outsider's interests in medical progress.

In addition to love, the family is best suited to help a child develop his or her own unique identity. As the Lindemann-Nelson's (2005) point out, families are particularly good at making

selves because they recognize the particularity and specialness of members in ways that larger institutions cannot (p. 37). As an example, consider how social clubs and churches can help to shape children's selves. Clubs and churches are by nature fairly large collections of diverse, unrelated individuals. They have primary purposes other than providing care and love. A club may want to engage in certain civic or social projects, while a church may be most concerned with articulating its particular theological distinctives and practices. Children can gain some sense of who they are from their participation, but these institutions can never provide the intimate, particular attention a child needs to truly develop a sense of self. Through their interactions with family members, children come to see themselves in relation to others and to identify what makes them unique. They also come to share in the family's history and current activities, understanding that they now have a place among their family's generations (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 39). Nothing can replace the early, profound sense of belonging and being loved that comes from a healthy family unit.

Helping a child develop a sense of self requires the judicious use of parental power. Shaping and pruning cannot be done unless parents have the power to exercise authority and discretion over their children and the various aspects of their lives (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 37). At the same time, children's agency is also important both in childhood itself and in the process of becoming a fully-functioning adult. The quality of one's life at all stages and one's endorsement of various decisions contribute to well-being. Childhood is often seen as merely a process of moving toward adulthood, but childhood is also valuable in itself. In fact, some goods and opportunities may even be more valuable in childhood (i.e. innocence, wonder, etc.) than adulthood. Once one takes on adult responsibilities, life changes (Brighouse and Swift, 2014, p. 65).

Yet, parents are also specifically tasked with raising children who will become minimally independent agents in the world (Brighouse and Swift, 2014, pp. 63-4). Society needs families to raise morally responsible adults who will broadly contribute to the world. Children must then develop a sense of healthy separateness as they mature. Parents are thus expected to share their power as children grow. Children gradually begin to have relationships outside of the family and to pursue their own interests and projects. Eventually, they develop a realistic self-concept and enjoy the goods stemming from knowing who they are and discovering where they belong (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 39).

As children learn what makes them separate and unique from others, they also learn to appreciate other people's separate and unique needs and desires. The family socializes children from being completely self-centered at birth to recognizing their interdependence. Children learn that others are persons too and should be accorded respect (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 40). In this way, virtues really are initially, as the Lindemann-Nelson's point out, "learned at our mother's and father's knee" (1995, p. 77). The family context provides a living laboratory for practicing virtuous moral conduct. Children must navigate a variety of family relationships and learn to meet their own needs while remaining sensitive and attentive to others. The values and principles we learn from our early experiences in the family become part of our developing moral conscience (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 79), helping us to discern what to do in difficult situations. Families then are important not just because they can provide children with protection and love but because they can help each child develop a sense of self and a moral conscience.

Thus, the discharge of parental responsibilities requires that parents ask their children to make certain sacrifices at home and for others. But, protection and love remain the foundational

blocks upon which moral behavior is cultivated. Since phase 1 trials are often presented as a way of helping others, enrollment could be a way to meet parental obligations by encouraging moral growth and behavior. At the same time, we must consider whether parents' other obligations might supersede their need to encourage selfless sacrifice.

Adults are not the only ones with obligations when it comes to children. Children's interests in developing their capacities and becoming fully functioning adults along with their need to enjoy the goods of childhood shape the social roles and responsibilities assigned to them. Obviously, I am not arguing that children have morally binding responsibilities in the same way adults do, but they do have important roles to play that are assigned to them by family members and by society more generally. Here, I argue that children have three primary social roles to play. They are expected to be obedient, carefree, and future-oriented in accordance with their age and developmental capacity. In the aggregate, they are expected to grow up and to imagine a life for themselves as they mature.

Because parents must exercise their power to protect and nurture children, children have a duty to cooperate through their obedience. When a parent gives a reasonable set of instructions, children are expected to follow them. Children may not always understand the reason for these instructions, but the expectation is that they will come to appreciate their parents' wisdom as they mature. Society also expects children to not be engaged in complex decision-making processes. This is in part because children are supposed to remain innocent and carefree. There is something unsettling about children who know too much of the adult world because childhood is a time during which children should not have to worry and fret. They will have plenty of time to see the wrongs in the world when they become adults. This is not to say that children are always

carefree. A variety of life circumstances can make children far more adult-like than they should be, but there is I believe a general idea that children should not have to worry about adult issues.

Finally, children are supposed to be future-oriented. Children go to school, learn new skills, participate in activities, and build relationships with the expectation that these will benefit them later in life. Of course, such pursuits are valuable in and of themselves, but adults often associate what children do now with the kind of future they will have. This future orientation is obvious if we simply think about how adults and children often interact. It is not unusual for an unfamiliar adult meeting a child to inquire about their favorite subjects in school or what they want to be when they grow up. By the time a child reaches middle school, questions about high school, college, and career become more frequent. It would be unsettling if a child replied that he simply did not think about or care about the future. It would be even more unsettling if he said that he thought he might not have any future at all.

In the final analysis, then, the family as an institution is partially justified on the basis of its capacity to love and protect children so that they can flourish during childhood and eventually develop into moral social agents. Brighouse and Swift go so far as to say children have a right to a parent insofar as they have a right to have someone who can bring about the goods of family life for them (2014, p. 66). On the other hand, the family is also justified by adults' interests in being parents. Children's needs may have moral primacy, but adults benefit in significant ways that cannot be duplicated through other relationships. After all, intimate relationships give life a great deal of meaning. A parent-child relationship provides a unique opportunity to meet a child's current needs while developing her future capacities (Brighouse and Swift, 2014, p. 88).

Parenting is special because it so encompassing. The parent has a great deal of power that she must wield as a fiduciary of her child's interests. These interests are partially shaped by the parent herself insofar as she shapes the child's eventual values. Parenting is a particularly emotionally and morally demanding enterprise that fosters significant opportunities for personal growth. Finally, the quality of intimacy is particular to parenthood. Parents and children love one another in deep ways not found within other intimate relationships (Brighouse and Swift, 2014, pp. 88-91).

Brighouse and Swift (2014) go on to describe when outsiders have an interest in intervening in the parent-child relationship based upon both respect for the good of families and the needs of society. While they are focused on public policy decisions (i.e. access to education, the free exercise of religion, etc.), their clarification of what should be respected about the parent-child relationship provides a model for what aspects of the family should be preserved and how to respect families while promoting their well-being. We will return to this idea of respecting what is valuable about the family in the context of phase 1 trials at the end of this chapter and in the next chapter. Yet, there is still the issue of how to balance interests when there are significant conflicts. In the next section, I take a look at how medical professionals judge family actions and whether the best interests standard can provide us with a way of mediating potential conflicts.

The Best Interests Standard and the Value of Families

Rather than justifying decisions involving families on the basis of both children's and parent's duties and mutual need for one another, medical professionals often turn instead to the best interests standard. Here, I wish to examine the best interests standard because I believe it is

often in contrast to how families actually operate. Simply put, the best interests standard requires parents to make choices that promote their children's aggregate long-term interests. By its very nature, the best interests standard and its application vary according to who is doing the deciding. It means different things in different circumstances and at different times in history. There has never been one legal standard for every case, so the courts have often used the standard as they see fit in each case.

The inherent tension within the best interests standard comes from the need to acknowledge the child as an individual while also understanding his social role in the family. If, practically speaking, ought implies can, then we cannot ask parents and children to do things that are not possible in their real-world context. It is too simplistic to think of the child as an entity unto himself, but it is also wrong to imagine that his interests are never in conflict with legitimate parental needs and desires. Families have to act in the best interests of all members. In the next paragraphs, I focus on three possible definitions of the best interests standard, as articulated in a historical review by Kopelman (1997).

First, there is what I will call the minimal definition of best interests. A minimal definition of best interests only considers a child's most basic needs. In fact, this version of the best interests standard can more adequately be described as a harm prevention standard. This definition can be found in Doug Diekema's 2004 article arguing that the possibility of actual harm to children should be the standard for state intervention when parents refuse medical interventions. Diekema (2004) is legitimately concerned with how unclear ideas of best interests can result in the government needlessly disrupting family life. While we can all agree that harm is undesirable, we do not all agree about how to manage less serious interests. Rigorously

promoting children's supposed "best interests" can give rise to contradictory outcomes, and some of these outcomes may prove more detrimental than helpful to children.

Imagine a situation where a parent has a brilliant young child who has moved quickly through school and been admitted to an Ivy League institution far from home. The parents decide that the child cannot go away to school prematurely because they have jobs and a stable life with the child in question and his brothers and sisters in their current city. If we were to decide that an Ivy League education is in fact in the child's best interests (which many people might be likely to think), we might be able to justify either shaming the child's parents into moving to promote his good or removing the child from his home and allowing him to live with foster parents near the college in question. Of course, a reasonable solution would be for the parents to meet their child's needs in a different way that might not be in his ideal best interests but keeps the family together.

Or, consider a more mundane situation. Traffic accidents remain a serious cause of death in the United States, so one could argue that a child is safest if he does not travel by car unless the trip is directly related to his interests. Now, imagine a mother who wishes to go to Starbucks to get a cup of coffee simply because she needs to get out of the house and loves Starbucks. The child's interests would not be promoted by her trip, so we could say that she should not go out. But, it would be ridiculous to suggest that she forego every need or desire she has. The family is collective, not individual. Each member will sometimes have legitimate interests that conflict with other members' ideal interests.

The best interests standard requires key assumptions about what constitutes a child's legitimate interests to be made, and these decisions can be questioned. A harm standard seems

more easily enforceable in practice, as we are more likely to agree on what constitutes fundamental harm (i.e. starvation, physical deprivation, etc.) than what constitutes the good. Even when it comes to harm, members of society may still have significant disagreements though. Consider the decision of whether to play youth football or pursue a less risky sport. Playing football puts a child at increased risk for concussions and potentially permanent neurological sequelae. But, try telling parents that their children should not play football to minimize harm. It likely would not go well. Children also gain significant benefits from playing a team sport, the chance to pursue a college scholarship, and the opportunity to bond with parents who have similar interests. For better or worse (and I would argue for the worse), we allow parents to enroll their child in football programs because we have decided that the harms are not severe enough to prevent it. So, we need to ask and answer a similar question about phase 1 trials. Are the harms too great or can they be mitigated? I will return to this in the final chapter.

At the same time, a harm-based standard does not capture the fundamental moral duties of parents very well. Here, it is important to note that I do not believe Diekema (2004) is making any larger statement about what constitutes good parental behavior. He is concerned with drawing a line for when the state ought to intervene. At the same time, focusing on the minimum requirements for parents, though perhaps legally expedient, does not give us a full picture of how parents act for their children. It tells us surprisingly little about how normal families function, so it does not help us when the situation is more difficult. As such, it does not help us call parents to their greater moral responsibilities. The judiciary needs to set minimum legal standards, but we, collectively, need to expect more from parents than the mere absence of harm.

A harm-based standard does little in helping us think about the phase 1 context or supererogatory moral responsibilities. Parents contemplating phase 1 trial enrollment normally

have not neglected their parental responsibilities. They are trying to make the least harmful choice in a difficult circumstance. Ironically, a harm-based standard could be seen as a reason to impose burdensome experimental treatment on children. Death is an undoubtedly great harm, and most other harms would pale in comparison (though I will take issue with this assumption in later chapters). If phase 1 trials are a reasonable option to avoid death, then it would seem that parents have a duty to enroll. Of course, I would argue that phase 1 trials are not a truly reasonable option because they can actually be harmful while providing no realistic chance of benefit; but a harm-based standard of best interests could in fact drive parents to seek burdensome experimental treatment. A harm-based standard of best interests works in clear cut cases (i.e. abuse, neglect, etc.), but it does not help us much here.

Rather than a strictly harm-based standard, some theorists have called for an expansive or ideal notion of the best interests standard. Kopelman (1997) summarizes this position well in a 1997 article, though she herself does not advocate it. Under this form of the standard, we establish *prima facie* duties in accord with the general things children need. Parents or the larger society may never be able to fulfill all of these needs, but the ideal of best interests is what we strive toward in policy-making. This version of the best interests standard is not particularly helpful in our case because the situation is far from and can never be made ideal. But, even if the situation was better, parents could still never simultaneously meet all of their children's interests. While advocates would admit parents can never meet the ideal, their position provides frustratingly little guidance on what to do outside of a theoretical ideal.

As a non-medical example, consider the educational trade-offs parents make when they have multiple children. Having a sibling is usually a positive experience for a young child whether or not the siblings remain close in adulthood. Having a sibling helps children learn how

to balance their needs and the needs of others while providing another source of love, affection, and support in their own lives. At the same time, each child adds additional financial obligations. Imagine the case where parents are deciding whether to send their extremely gifted young child to the best private school in the city or to add to their family and send all of their children to a good, but not great, neighborhood public school. The child has an interest in both of these outcomes, but only one is feasible for the family. Or, consider a parent who foregoes some opportunity for her child so that she can have a break and do something for herself. There is nothing wrong with her doing this (On the contrary, it is probably very good.), but she cannot possibly be promoting the best interests of her child in an ideal sense. An ideal standard is impossible to meet with multiple people who have competing interests involved in the situation. Yet, this situation is exactly what families face each and every day and part of what makes families good places for children to develop into responsible citizens. Simply admitting that the standard is theoretical and practically unattainable does not say much about how people should balance their children's interests within the family context.

As a medical example, consider the phase 1 trial in pediatric oncology. Clinical trials for different types of cancer occur in various locations around the country. How far from home, work, and other family members should parents have to travel to enroll? How much evidence of benefit is required before families must relocate and give up their stability? When the stakes are particularly high, an idealized version of interests can destroy the family unit for the sake of providing some minimal or imagined benefit to one member. Yet, destroying the family in the service of one individual is quite harmful too.

As an intermediate standard between the extremes of the minimal and the ideal, Kopelman (2010) proposes that an individual's best interests be considered according to the

guidelines of reasonableness. She suggests, "First, decision makers should use the best available information to assess the incompetent or incapacitated person's immediate and long-term interests and set as their prima facie duty that option (or from among those options) that maximizes the person's overall or long-term benefits and minimizes burdens" (Kopelman, 2010, p. 25). "Second, decision makers should make choices for the incompetent or incapacitated person that must at least meet a minimum threshold of acceptable care; what is at least good enough is usually judged in relation to what reasonable and informed persons of goodwill would regard as acceptable were they in the person's circumstances" (Kopelman, 2010, p. 26).

At first glance, this version of the best interests standard seems the most intuitively reasonable. However, it leaves major questions open about how to balance benefits and burdens as well as what considerations should be taken into account by the "reasonable and informed person of goodwill." I would argue that most parents are trying, within the limits of their knowledge and abilities, to promote their child's long-term health and well-being. The reasonableness standard does take a step in the right direction by requiring that burdens be minimized, but it still gives little guidance about how to weigh benefits and burdens. And, whose considerations should parents listen to? They can listen to a variety of voices- the physician who says that the phase 1 trial is at least not giving up on the possibility of cure, the other physician who recommends hospice care, the patient advocacy groups who make it their mission to push science forward in the service of future patients, or the larger society with many voices that especially prize and have a vested interest in scientific contributions. Kopelman's (2010) criteria for decision-making provide some guidance on how an idealized version of the best interests standard might apply when interpreted by a court or other disinterested outsider, but she has not moved us significantly toward a more holistic model for parental action.

Promoting Children's True Interests within the Family

The best interests standard is a morally haphazard standard for judging parental decisions, especially when options conflict and situations are complex. The best interests standard does work in clear-cut or so-called "black and white" cases. For instance, no reasonable person would argue that a child should be subjected to avoidable pain. Parents who purposely caused pain or refused medical efforts to treat pain would not be acting in their child's best interests. However, it is my contention that the social world expects parents to be generally responsible for their children rather than simply meeting a legal standard of promoting their "best interests." Parents should be primarily judged on the unique goods they bring about through family life. Parents who protect, love, and shape their children into mature adults are fulfilling their obligations. These duties will sometimes result in conflicts, but a parent who is attempting these three feats cannot fail, even if she finds it impossible to simultaneously meet every single interest a child has. To intervene, whether formally or informally, on any basis except to insure the goods of family life for each child is to overreach and to forget what is so intrinsically valuable about families in the first place.

We must now turn to the question of how parents can bring about the goods of family life in the face of serious illness. Families remind us who we are when we are sick and may feel estranged from ourselves (Lindemann-Nelson and Lindemann-Nelson, 1995, p. 45). Especially when they are in an institution, children need to be reminded of who they are and how valuable they are. Seriously ill children may very well not survive to adulthood, so the need for safety and well-being becomes primary. Parents need to be given resources and opportunities to responsibly exercise their authority at the end of life in ways that allow them to protect, love, and shape their children. Parents should be given opportunities to protect their children from pain and grief as

well as to help them cope with these burdens. Parents and their child need to be intimately connected and to reassure one another of their love and devotion. Parents must also share their power to the extent feasible with their children. Part of parenting a seriously ill child is letting go and recognizing that the child will not have the kind of future other children have. The decision, then, of whether to enroll in a phase 1 trial can be judged according to whether it allows parents to protect, love, and shape their children while promoting a close relationship between parent and child. If a phase 1 trial does not allow these goals to be met, then it cannot be considered a reasonably good decision.

Part of growing as a parent is to endure the hard times, and parents truly need to be fully informed and discharge their responsibilities when their children are very ill. Even though we may see death as the end of the parent-child relationship, being a parent is an identity that lasts for life. Parental emotional and moral growth remains a priority even when the situation is extremely trying. Parents and children need each other as much at the end of life as at the beginning of it. The fruits of their relationship can be good for both participants, but realizing those fruits requires honesty about what both parties are facing. To obfuscate or minimize parental duties at the end of life is to deny parents the opportunity to define and develop a new role as well as to deny children the chance to share their true feelings and be reassured of their family's love and acceptance. The decision to participate in phase 1 trials should be judged according to whether it brings about the goods of family life. If it does not, then phase 1 trials will need to be modified in order to remain a viable option.

Concluding Remarks

In this chapter, I have argued that parents are charged with protecting, loving, and shaping their children into persons who have a healthy self-concept and regard for others. Children are to fulfill certain social roles by being obedient, remaining carefree, and focusing on the future. Parents have an interest in being parents because they have an interest in the special type of relationship one has with a child. Parenthood requires growth and sacrifice in ways that other intimate relationships do not. After all, in no other relationship do you have the responsibility of loving and protecting someone who will eventually separate and become her own person.

While the best interests standard is by its nature vague and all-encompassing, families have very particular obligations. Judgments about parental actions should consider whether parents are protecting, loving, and shaping their children rather than whether they are meeting every obligation an outsider might think a child has. Judgments about the good of enrolling children in phase 1 trials must come through examining whether such enrollment actually brings about the goods of family life so crucial when children are very ill and vulnerable. In the next chapter, we will turn first to how families experience having a child who is very ill. Then, we will examine how they come to a decision to enroll in a phase 1 trial and the extent to which they can continue to protect, love, and shape their child after enrollment. Finally, we will consider the counter-argument that enrollment allows families to maintain their hope and autonomy rather than giving up on a cure.

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Chapter Four

Parents and Children at the Bedside

In the previous chapter, we moved away from considering regulations and into the social and relational context in which early phase research trial enrollment happens. Parents and their children have relational interests and obligations, and physicians also have relational interests and obligations when they interact with families. First, I focused on parent-child relationships because parents are usually charged with making decisions for their children. I argued that family actions and decisions are best judged on the basis of what is intrinsically valuable about the family- that is, what relational goods families are especially suited to bring about for children. But, critical illness can change family dynamics, so it is crucial to now consider how parents and children experience and understand illness trajectories as well as why they enroll in phase 1 clinical trials. Then, we can consider whether such decisions enable parents to protect, love, and shape their children in an end-of-life context. We will also consider whether children can continue to play socially accepted roles at the end-of-life. If we find that parents and children cannot continue to fulfill their roles and obligations, then we will have to consider alternatives to the phase 1 trial in a later chapter. Finally, we will consider the argument that phase 1 trial participation in its current form empowers families by helping them remain optimistic and hopeful when facing a child's grave illness.

What Seriously Ill Children Know and Experience

Any discussion about children and adult interactions in the phase 1 context must begin with an analysis of how much children know about their illness and what sensitive topics they can handle. Since the parent-child relationship is primarily justified by children's needs, we need

a better understanding of how they articulate their understanding and what they perceive to be their needs. Common arguments made in favor of non-disclosure or for children not participating in the research assent process are their inability to truly understand what they face and the stress of discovering they are very ill.

But, these assumptions are questionable. In her 1980 seminal work, *The Private Worlds of Dying Children,* Myra Bluebond-Langner chronicles how children and their parents respond to cancer from diagnosis to remission or disease progression and eventually even to the end of life. Bluebond-Langner challenges the notion that children simply do not understand their illness and cannot modify their behaviors in response to it. Childhood is not simply the process of absorbing external inputs and becoming an adult. Rather, it is a unique phase of life that, while usually leading to adulthood, has its own values and norms. Socialization is a two-way process between the child and her world (Bluebond-Langner, 1980, p. 5). Because children are always learning from the adults in their lives and the larger world, they possess varying degrees of qualities we often see as adult-like, though they may express them in different ways. To summarize her framework, Bluebond-Langner makes the following points regarding children as they grow and develop:

1. They are willful, purposeful creatures who possess selves.
2. They interpret their behaviors and act on the basis of their interpretations.
3. They interpret their own self-images.
4. They interpret the behavior of others to obtain a view of themselves, others, and objects.
5. They are capable of initiating behavior so as to affect the view others have of them and that they have of themselves.

6. They are capable of initiating behavior to affect the behavior of others toward them.
7. Any meaning that children attach to themselves, others, and objects varies with respect to the physical, social, and temporal settings in which they find themselves.
8. Children can move from one social world to another and act appropriately in each world. (1980, p. 12)

With these premises in mind, Bluebond-Langner observes that children both sense and often understand the basics of their illnesses, the hospital hierarchy and social context, their parent's emotions, and the behaviors that are expected of them. Regarding children's knowledge of their illness, there are several instances when Bluebond-Langner observes them speak freely to one another. When the children are left alone with other patients, they frequently discuss medications and their side effects, though they do not engage in discussion in front of adults. For instance, several children coloring during a clinic appointment were readily able to identify which medicines they take in the morning and their side effects.

OTS [Occupation Therapy Student] 1: What did you all have for breakfast today?

Lisa [7-year-old leukemia patient]: I had some juice and cereal and cytotoxin.

Michael [another 7-year-old leukemia patient]: I had juice and eggs and cereal and prednisone.

Lisa: That's why you eat so much.

Michael: I know, it's [the prednisone] like a tapeworm. (Bluebond-Langner, 1980, p. 56)

In another scene, children are being weighed in an outpatient clinic and converse about prednisone's side effects.

Lisa: No! I weigh the same as I weighed before, eighty-three pounds.

Sharon [a staff member]: You look like you've gained ten pounds.

Sandy [six-year-old boy with leukemia]: It's that prednisone. It does things to you.

Sharon: What does it do?

Jeffrey [5-year-old leukemia patient]: It makes you eat like a pig and act like a brat. (Bluebond-Langner, 1980, p. 61)

As their disease progresses, the children learn the routine of trying new treatments, relapsing, and then trying again. They explain the journey quite succinctly.

Jeffrey: (*Sitting and staring at the lump of clay in his hand.*) The yellow medicine was supposed to last two years, but it only lasted seven weeks. Now I have the red medicine, but it won't last as long as the yellow.

Peter [a new patient transferring from a previous clinic]: (*Shaping pieces of clay into little balls that resemble pills.*) I take ten of these (*pointing to the already finished balls*), each day, but today they are going to change my medicine.

Jennifer [7-year-old leukemia patient]: (*Looking up from the animal she is molding*.) They have to do a bone marrow first.

Peter: How do you know?

Jennifer: You'll see. Then they wait four weeks and give you another bone marrow and another medicine until that one stops working and then they start again. (Bluebond-Langner, 1980, p. 87)

Children also provide support to one another through a cycle of relapses and remittances- good times and bad times.

Jeffrey: What's a relapse?

Jennifer: That's a bad time. There are good times and bad times. It's usually when the medicines aren't working and your body is sick again. (Bluebond-Langner, 1980, p. 104)

Eventually, as the condition of some children worsens, they begin to understand the possibility of death, attempting to confirm their suspicions with staff members. In one scene, Tom, a 7-year-old leukemia patient, reacts to Jennifer's death the previous night.

Nurse Barton: Tom, would you like to go down to the playroom?

Tom: (*Turns over*) Uh huh. (*Pause.*) Jennifer died last night. I have the same thing, don't I?

Nurse Barton: But they are giving you different medicines.

Tom: What happens when they run out?

Nurse Barton: Well, maybe they will find more by then. (Bluebond-Langner, 1980, p.120

Despite reassurances, children begin to acknowledge that they know death is at least a possibility, if not an inevitability. Mary, an 8-year-old leukemia patient whose parents opted not to reveal her diagnosis to her, still shows she knows she is ill and even acts out death scenes.

OTS 3: …What should I do with these [paper dolls]?

> Mary: Put them in their graves, in the Kleenex box. Let me do it. Bring it over here. (Bluebond-Langner, 1980, p. 117)

As children came to understand that they were becoming sicker and approaching the end of their lives, Bluebond-Langner observed that they became less interested in the outside world. They no longer acted as people who would grow up. The future seemed less relevant (Bluebond-Langner, 1980, pp. 192-94). Children even recognized that the pain and suffering of treatment may be for naught in the end. As one put it:

> My friends' relapses worry me sometimes, because they thought that one day they could be sure and that they could go on with their lives and it didn't turn out that way. So, once in a while I think maybe I will relapse and I won't be around very long. It makes me wonder if I should just give up chemotherapy altogether and live my life the best I can for a couple of months or whatever. Or maybe I should just go out and have a good time, because you really don't know what the future holds. (Bluebond-Langner et al., 2010, p. 333)

Gradually, children begin to give up the fight- to accept death's inevitability. In perhaps the most moving paragraphs of Myra Bluebond-Langner's book, she describes how Jeffrey Andrews, a leukemia patient now at the end of his young life, asks her to read from the book *Charlotte's Web*. Interestingly, he specifically asks to read the part of the book where Charlotte dies. Bluebond-Langner reads to him as he doses off, and Jeffrey himself dies a short time later (1980, pp. 128-34).

Despite their recognition of this monumental change in their lives, parents and children often go to great pains not to directly recognize reality- a phenomenon Bluebond-Langner

discusses as "mutual pretense." In mutual pretense, both parents and children are tacitly aware of the disease course, but both believe they should not speak of it. Difficult or emotional topics are avoided. This makes decisions about end-of-life care particularly difficult because neither party will forthrightly communicate with the other. Things appear to continue normally, and any deviations from normal go unacknowledged. If uncomfortable topics cannot be avoided, withdrawal from the situation or significant persons occurs (Bluebond-Langner, 1980, pp. 201-07). One thing is clear- neither party wants to bring emotional pain to the other. Parents naturally feel protective of their children, and children also desire for their parents to be happy. For instance, Jeffrey Andrews, the 5-year-old leukemia patient whose family is featured in Bluebond-Langner's work, understands his mother's emotional distress and even identifies himself and his condition as the cause of it.

> Myra: Hi, Jeffrey.
>
> Jeffrey: (*Puts down the stamper*) See my mommy's red nose? That's from me. That's from crying. Everybody cries when they see me.
>
> Mrs. Andrews: Oh, Jeffrey. (*Aside, to Myra)* I try not to cry in front of him. But he knows…(Bluebond-Langner, 1980, p. 34).

All of Bluebond-Langner's observations show that children come to know a great deal about their illnesses and how their being sick affects other family members, even when information is purposely withheld. Children who have struggled with an illness for a prolonged period develop much more competence related to health care and medical decision-making than other children at the same age and developmental level without experiences of serious illness. When children are not given the truth, they go to great lengths to fill in the gaps. They have even

been known to imagine a worse scenario or to believe their illness is a punishment for some perceived wrong-doing. Generally, children will discover the truth about how seriously ill they are whether there is open disclosure or not, but open disclosure gives them a chance to discuss their fears and concerns out loud (Cole and Kodish, 2013).

Especially as their illness worsens, children also struggle with questions about how much suffering is enough and the need to "just be a kid" in the face of grave illness. These sentiments were perhaps best expressed by the teenager talking about whether she should just enjoy life for the time she has left (quote on p. 102). Failing to fully disclose information about their illness or about the reality of participating on an early phase experimental protocol where cure is no longer a likely or reasonable goal does not promote children's long-term interests or give them an opportunity to express their own wishes. Efforts to "protect" the child and foster the belief that a clinical trial is just another therapeutic effort are misguided. Children can become even more anxious when they do not understand but know that something is very wrong, and they already sense they may not have the same future as their peers will.

What Parents of Seriously Ill Children Know and Experience

Parents with seriously ill children go through their own trajectory of understanding. This trajectory varies depending on the gravity and nature of the child's illness; however, we will focus on the time when children have relapsed and little hope of cure remains. Parenting a child throughout the end-of-life course can be described sequentially, and parents move through distinct phases as they process information. First, parents must come to the realization that their child's death is inevitable. Then, they can begin to focus on making the child's remaining time enjoyable while continuing to preserve the parent-child relationship. Finally, parents must

manage the child's deterioration for the better, and when this is no longer possible, they must simply remain by the child's side until death comes (Kars et al. 2011).

We know far more about what parents want as their child approaches the end of life than we know about what children want. Parental needs and wants at this stage can be summarized in four categories: the importance of protecting the child, the establishment of normalcy and control, the need to be a "good" parent while meeting personal and social expectations associated with the role, and fulfilling the role of parent as a bearer of hope to the very end. Just as children start to think less about the future, parents also become more focused on day-to-day and moment-to-moment existence.

When a child is seriously ill, parents are thrust into a new world that requires them to deal with their child's significant suffering. They respond to their child's real physical and emotional vulnerabilities by becoming more protective and guarding the child against negative experiences and beliefs. Parents also try to preserve the child's self-perception and hope for the future by influencing the child's ideas about his illness and future survival, especially by encouraging the child to cooperate with treatment. Cooperation with the treatment team is perceived as necessary for the child's self-preservation, so actions that demonstrate the child's compliance are purposely rewarded (Kars et al. 2008). Parents are no longer in a role of fostering growth and development in the actual world. Instead, they view the actual world as extremely threatening and their influence as providing a safe haven for their child.

Yet, parental desires to protect their children from pain and suffering are often frustrated by frequent medical interventions. In some of Myra Bluebond-Langner's (1980) conversations, parents demonstrated a sort of learned helplessness because they could not protect their children

from medical pain and procedures. In a scene with Mrs. Welder, the mother of Faith Welder, a three-year-old leukemia patient, we see Faith's mother standing by helplessly as doctors treat her daughter's painful abscess. Faith is screaming and thrashing as surgeons work.

> Faith: (*Cries, opening and closing her outstretched hands*) Mommy! Mommy! Mommy! Mommy!
>
> Mrs. Welder: (*Does not look at Faith, but buries her head in her hands, then looks alternately at the ceiling and the floor*)…(p. 35)

A nurse comes in to ask if the mother needs a glass of water and escorts her out of the room.

> Mrs. Welder: (*Outside of the room with Nurse Lockner*) It's times like this when I think about what she knows, and I know how sick she really is. She's in there screaming her head off, and there's nothing I can do! (p. 36)

The desire to protect their particularly vulnerable child is one mechanism by which parents maintain normalcy and control in the parent-child relationship. Spending as much meaningful time together as possible and maintaining the normal parent-child relationship are very important to families at the end of life (Zaider et al., 2015). When we think about the normal range of parental experiences, parents are often the ones to comfort and soothe a crying child and to protect them from painful experiences. But, parents whose children have end-stage cancer have gone through a process where they have had to partially give up their role as protector. Holding a child down for procedures, performing medical procedures at home, or simply agreeing to a procedure involves parents in uncomfortable situations where their children experience pain and fear. Of course, these procedures are at first necessary and for the child's benefit. However, at a certain point in time, burdensome procedures actually become harmful

and unnecessary. By this time though, parents are used to permitting temporary pain and discomfort for future benefit. They have likely gone to great pains to promote their child's compliance. In experimental situations, aggressive procedures unlikely to be beneficial may continue under the guise of the child's future benefit. This situation is not the parent's fault but the result of a change in parental role caused initially by medical necessity and later by the medical environment. Parents are fooled because they have become so embedded in the medical context that they do not make the transition from understanding intervention as a matter of their child's self-preservation to the understanding of intervention as a sacrifice for future patients. After all, procedures are familiar and do not look different when they are done for clinical benefit or scientific necessity.

Parents usually want to do far more than protect their children. They want to be "good" parents. When asked how to be a "good" parent to a child with cancer at the end of life, parents identify making informed, unselfish decisions in the child's best interests, remaining at the child's side, showing the child that she is cherished, teaching the child how to make good decisions, advocating for the child, and promoting the child's health as important aspects of their definition. Even near the end of life, parents continue to want to fulfill all of the essential parental roles (Hinds et al., 2009). They want to protect, love, and shape their children, but they need assistance in deciding how they can meet these goals. A phase 1 trial is one way parents can try to be "good" parents; but, I will question some key assumptions about this course of action in this chapter's next sections.

Finally, parents feel that they must be bearers of hope, but there are a variety of ways that they play the role of hope bearer. To start, it is important to understand that hope is not solely related to length of life or the possibility of cure. Parents often report wanting honest

communication, more time with their child, and a truthful discussion of prognosis (Heinze and Nolan, 2012). They clearly want to know what is possible- that is, what can be hoped for. Parents even expressed the capacity to continue hoping for a cure when they realistically believed that a cure was no longer possible (Kamihara et al., 2015). While the physician may lose hope in the face of scientific or medical data, parents need to maintain hopefulness. Parents can continue to bear hope in many ways even when cure is no longer a realistic possibility, and physicians can partner with parents to encourage more realistic hopes rather than presenting a failure to cure as hopelessness (Reder and Sewint, 2009). Parents can then acknowledge that their child is in fact dying, working to realize hopes related to the dying process. Obviously, these hopes are not what parents ideally or initially desired, but they are still realistic hopes that may in fact be fulfilled. Parents routinely identify both their future-oriented and present-oriented hopes. Hope can be maintained even when it only applies to the next day, hour, or minute (Granek et al., 2013) when parents know what can realistically be hoped for and have a concrete plan with the care team. Parents are then able to benefit from the realization of their secondary hopes even when their greatest hopes have been frustrated.

As a child's condition deteriorates, there is usually a tacit recognition, even if parents cannot bear to publically acknowledge reality. Parents often "know" deep down that their children will not be cured as the medical situation worsens. As one mother explained:

> It wasn't until we were in the hospital again this last time that it hit me that all of the other children had died. It wasn't until Lakshmi asked if she was going to the same place as Leah that I realized that all the time, all the treatments, we were just buying time. She wasn't going to be cured. I knew that, well, sort of, it was just too scary, or I just didn't

> want to think that she wouldn't be cured. But I knew deep down that she wouldn't be. (Bluebond-Langner et al., 2010, p. 333)

While the mother was not prepared to unilaterally act on the information, she may have benefited from the opportunity created if a physician approached her during a discussion about prognosis. Without such a discussion, a physician presenting the phase 1 trial option leaves parents in a difficult bind. If they bring up their knowledge, they may be perceived as giving up prematurely. If they stay silent, they risk subjecting their children to pain and suffering without adequate understanding. Parents also seem keenly aware that experiments can and do fail. One mother explained:

> We felt like telling him it's a clinical trial, but that sounds so harsh. We never did use the word trial. We didn't want him to think that it was some kind of experiment. You know, sometimes experiments don't work. He is only 13, 14 in three weeks. We just felt like this was something that he didn't have to know. (Bluebond-Langner, 2010, p. 335)

I would speculate here that the child probably already had some idea of his current medical state, and the parent clearly understands its gravity. It seems to be the public recognition that is so difficult. No one has yet helped parent and child to transition from cure-based hope to other types of hoping, and both keep quiet so as not to disturb the current equilibrium. The key then is determining if and how phase 1 trial enrollment can provide what parents and children need at the end-of-life, allowing them to fulfill their roles and duties until the final breath.

Why Parents and Children Enroll in Phase 1 Trials

Now that we have discussed the normal roles and responsibilities assigned to parents and children and considered how both respond in the face of critical illness, we need to consider why

parents and children normally enroll in phase 1 trials as a way of meeting their mutual obligations. Here, I focus on children insofar as they can give assent to trial participation and have their own ideas about what participating means. I aim to demonstrate that both participate in the hope of clinical benefit and that they often believe trial enrollment is the only way to continue receiving medical care. Parents do not usually consider enrollment to be a willful choice but a necessity. From the parents' perspective, those who opt for enrollment in phase 1 trials report a greater feeling of being compelled to enroll in the trial as a last-ditch therapeutic effort, believing that trial participation is the only acceptable way to promote their child's interests. There is incredible pressure to pursue every option that can make parents feel they have no real choice in the matter. Parents opting against enrollment more frequently reported feeling empowered to choose based on quality of life and the child's wishes (Maurer et al., 2010).

There are four primary points to be made here. First, parents have a poor understanding of what enrolling in a phase 1 trial really means and what the main purposes of these trials are. Secondly, parents usually consent on the basis of expected clinical benefit rather than for any other reason. Even altruism is usually combined with some notion of direct clinical benefit (Valdez-Martinez, 2014). In other words, there are few cases in the phase 1 context where children or their parents consent solely on the basis of altruism. Third, parents feel a great deal of social pressure but also a social responsibility to enroll in clinical trials. They do not want to let down the medical staff or other sick children who might benefit from the trial. Finally, they do not necessarily consent because they believe it is the best option for their child or will enhance their child's life but because they are rarely presented with alternatives.

To the first point, parents show very limited understanding of phase 1 trials' scientific purposes, usually viewing it as simply a continuation of their child's previous medical treatment

(Levi et al., 2000). In one study of informed consent conferences, only 32% of parents demonstrated an adequate scientific understanding of the phase 1 trial, including appreciating techniques like dosage finding or escalation, or identified the primary purpose of the trial as learning about drug safety. Thirty-five percent of parents demonstrated little to no understanding (Cousino et al., 2012). Parents have particular problems understanding randomization. In an analysis of informed consent conferences at six children's hospitals over a two-year period, Kodish et al. (2004) found that only 50% of parents understood what randomization meant despite the physician explaining the procedure in 84% of cases as well as the provision of informed consent documents. Another study found that parent could name few potential side effects from trial participation and also could not identify the overall scientific purpose of the trial (Chappuy et al., 2013).

In reference to the second point above, the hope for therapeutic benefit, maintained by the social environment, is a primary way parents can justify early phase research participation that they know may be burdensome for their child (Oppenheim et al., 2005; Unguru, 2015). Parents are rarely in equipoise regarding trial participation (de Vries et al., 2011). As one Canadian mother explained:

> I wanted her to get the most. I wanted to be sure that we killed this off. So I had to stay in the study to get the best option for my child. It wouldn't just offer that to her, without being in the study. It's like, ‘‘you can have this apple, but if you come over here, we'll give you apple pie.’’ Well I'm not an idiot, ‘‘let us go for the apple pie." (Woodgate and Yanofsky 2010, p. 14)

To the third point, parents feel a desire to participate for their children and for others. There is incredible pressure from society at large to participate in research that might help future patients. Even patient advocacy groups may pressure current patients to help find future cures (Woods et al., 2014). During the consent process, parents are often moved when told about how the research enterprise might impact future patients. One parent commented:

> They talked about how the success rate is now 80% to 85%, where 25 years ago it was lucky if it was 5% to 10%. And it is through these studies that just makes the treatments better. So when we talked, we thought obviously lots of other people that have done these, and it will get to the point where it is at now, which is that much better. So if we can help out…(Woodgate and Yanofsky, 2010, p. 14)

Another pointed out:

> It is relevant to society. It is relevant to future care analysis, of individuals which is why I did want to be a part of it. It is relevant to me as a parent who can prevent some other child getting care that they don't need, or get better care than they could have gotten because my child took part in the trial. (Woodgate and Yanofsky, 2010, p. 14-5)

Additionally, parents reported that they did not want to disappoint the physicians who were part of their child's care team. One parent worried:

> You know I was worried that I was going to let down this poor doctor. And I thought what is he going to think, like what kind of people are we? You feel bad and you hate making that decision, and you feel bad cause these doctors and nurses spent a lot of their time explaining everything to you. And you think they're going to be looking after us and we are not wanting to help them with their study. (Woodgate and Yanofsky, 2010, p. 15)

It is worrying that there is social pressure to enroll in trials or at the least a feeling that declining to enroll is a moral failure.

To the fourth and final point, parents routinely express dissatisfaction with physician discussions about alternatives outside of clinical trials. They may not be made aware of or empowered to choose an alternative. In one study, half to two-thirds of parents reported a lack of discussion about alternatives and a subsequent perception that the clinical trial was the only "treatment" option (Kupst et al., 2003). When given the choice between doing something and having no concrete plan for future care, it is not surprising that parents would choose the more action-oriented alternative. Parents are far more likely to choose palliative care when it is presented as doing something different rather than foregoing the chance to "do" anything. When they have a discussion with the medical team about what can be hoped for and the steps they can take to maximize quality of life, parents feel empowered to choose between alternatives (Valdez-Martinez et al., 2014).

Children actually vocalize many of the same concerns and questions as their parents. They too give assent on the basis of individual benefit or for a mixture of altruistic and individualistic motivations. In some contexts, adolescents appear willing to undergo minor, minimally risky procedures (i.e. blood draws, skin biopsy, etc.) in order to benefit others (Wendler et al., 2012). Yet, adolescents involved in phase 1 trials overwhelmingly consent due to hope for cure (Miller et al., 2013). In general, children tend to consent primarily on the basis of hope for cure or life extension with some altruistic intention as a secondary motivation (Valdez-Martinez et al., 2014). If a child occasionally comes to believe that his participation in a trial is not primarily for his benefit, he can rationalize it as still consistent with his best interests or because he believes he is specially selected due to the nature of his condition.

For instance, consider an ethnographic study in which children were asked about their participation in psychiatric clinical trials (Koelch et al., 2009). Most children believed the experimental drug was being tested to see if it helped them specifically and also so that other children might receive it in the future. Here, I think a brief flashback to the Ramsey-McCormick debate is helpful. McCormick might argue that children had the right idea here if they were not exposed to significant risks. They could help others and potentially receive some benefit from the trial. But, since the trial was not primarily designed for the children's benefit, Ramsey might argue that it would be inappropriate for children to consent on the basis of altruism alone. The whole trial would present ethical difficulties if the child subjects were not primary beneficiaries at all (a likely suspicion in most drug trials). Researchers would need to admit using children when they ought not be used and cede the powerful role of physician. In fact, children here appear to consent on the basis of personal benefit mixed with some secondary altruistic intention. When asked about the purpose of the trial, representative answers included:

> So that I feel better and just generally.
>
> Boy P, 12 years old
>
> That it helps me (...) and whether it helps other kids.
>
> Boy R, 10 years old
>
> Because if it (the medication) is not effective, and the medication is sold and the doctor in the pharmacy...ehm, if the medication does not work then, then people buy it and then they spend their money for nothing.
>
> Boy S, 9 years old (Koelch et al., 2009)

One boy seemed to understand that the trial's primary purpose was not his benefit but rationalized participation by explaining that he had been specially selected.

> I think I will be something like a guinea pig…Because, I'm something like a special case, because I'm really intelligent, I'm suffering from ADHD and at the same time from ODD and I also have dyslexia and because of me being a mixture of nearly everything (...).
>
> Boy H, 12 years old (Koelch et al., 2009)

Altruism was mixed into some answers.

> And, that it will improve the disease in others, and that it (the medication) also helps other children, because it should also help other children, not only me.
>
> Boy S, 8 years old (Koelch et al., 2009)

By and large, children believed decisions about group assignment and medication dosing or placebo use would be made with their interests in mind whether they could explain their inclinations or not.

> Interviewer: Who decides whether you will receive a placebo?
>
> „The psychologist
>
> Interviewer: (...) Do you think you will receive a placebo?
>
> Not really
>
> Interviewer: Why not
>
> Ehm because, in fact, I don't know, I don't have a reason.

Boy S, 8 years old (Koelch et al., 2009)

It is apparent that children have some of the same struggles as their parents in understanding the purposes of clinical trials. They are also likely to be excluded from meaningful discussion during the parental consent-child assent process. In one study of informed consent conferences, patient-to-physician conversation occurred for only 3% of the total conference time, and 10% of children were asked to sign the assent form without being asked about their actual opinion on trial participation (Miller et al., 2014). In another series of interviews with children enrolled in cancer-related phase 1 trials, 51% did not know that their treatment was actually research, and 86% did not understand their doctor during informed consent meetings. All children wanted some decision-making role, but half felt they had no role in deciding about trial participation. More than a third felt that they could not dissent (Unguru et al., 2010).

Fulfilling Parental Obligations and Children's Roles

We could at this point consider all of the ways we might practically improve the informed consent process. Researchers have after all produced detailed reviews of the process with suggestions from parents and children (Baker et al., 2013; Eder et al., 2007). But, to do this is to miss the larger question about the morality of phase 1 trial enrollment. These trials must be judged based on parental ability to meet their moral obligations and children's ability to continue their social role in the family. The preceding information provided about how parents want to protect, love, and shape their children's experiences when facing serious illnesses and children's needs provides us with a context for evaluating whether phase 1 trial enrollment helps parents fulfill their responsibilities and children to play their social roles within the family. We need far

more than an improved informed consent process here. The problem is not with informed consent but with the ethical reality of phase 1 trials in their current form.

To begin, I consider the parental responsibilities of protecting, loving, and shaping. It appears to me that phase 1 trials in their present form are not in fact a way of allowing parents to truly protect, love, or shape their children, though they may be a way to avoid reality. After all, what parents report they want through enrollment in phase 1 trials includes minimum physical restrictions, normalcy and control, information sharing, and having hope for life (Barrera et al., 2005). Regarding physical and emotional protection, it is unclear that a phase 1 trial promotes either of those efforts. Trials often involve burdensome procedures and the risk of increased physical suffering from toxicity. Sometimes, participation in a trial requires the child to remain hospitalized- an environment where parents often feel they cannot protect their child. Emotionally, the continued emphasis on battling cancer can isolate children and make them feel alone with the secret knowledge that they are very sick and likely dying. They may maintain "mutual pretense" to protect their parents rather than the parent in fact protecting the child from emotional distress. Some of these conditions might be remediable, but such remediation would require significant changes as discussed in the final chapter.

Turning to the parental duty to love, it is obvious that parents are acting from a sense of love, but enrolling in a burdensome trial may preclude better opportunities to connect with and love their child. A loving relationship must be intimate and honest because true intimacy requires honesty when facing challenges together. If the reality of illness and likelihood of death are not acknowledged, parents and children remain unfree to ask difficult questions and truly comfort each other. Enrolling in a phase 1 trial is only acceptable if burdens are low and parent-child honesty is high. I argue that parents would in fact only accept low-burden trials if they truly

realized their child was not the trial's intended beneficiary. The realization that phase 1 trials are not treatment options would undoubtedly cause pain. Yet, even in moments of pain, true intimacy can bring satisfaction. Children need to know that their parents' love is unconditional and that they will still love them even after they die. Parents need to know that their children are loved and know they are doing the best they can. Maintaining a loving bond at the end of life requires honest disclosure, and pursuing a phase 1 trial usually obscures reality. A phase 1 trial allows both parties to keep fighting and in that way does not allow them to resolve existential fears about life and death. Recognizing the trial as a pure sacrifice allows parents to consider family disruption and the child's quality of life. Parents likely enroll in phase 1 trials out of love, but we owe it to parents to give them better opportunities to love their dying child- to remind their child who they are in the family until and after their last breath in this life.

There may be occasions where parents see the downsides of trial enrollment, and those in favor of phase 1 trials may argue that enrollment still provides a way for parents to shape their children's moral character. Overall, clinicians tend to bring up altruism more often than families, but some families have raised altruism in recorded informed consent conferences (Hazen et al., 2015). However, there is a powerful argument to be made against the position that altruism can justify risks from phase 1 trials. Children dying from cancer likely never come to understand their contributions or to see their fruits later in life. They usually do not have much say in trial enrollment and operate under many of the same misconceptions as their parents. The true shaping of character requires sacrifices to be fully understood. A child cannot grow morally from what he does not understand. But, critics might argue, perhaps the child will come to understand at some later date? David Wendler (2012) makes a powerful argument in favor of non-beneficial research by arguing that children can later come to appreciate their participation and to live a

better life because they have participated in charitable activities. However, his argument assumes that children must be alive long enough to come to appreciate their sacrifices. This is unlikely among pediatric cancer patients enrolled in phase 1 trials.

Perhaps, phase 1 trials can be justified by allowing children to play their roles in the family even as they near death. Children may be able to remain basically obedient to their families by participating in a phase 1 trial that their parents have selected for them; but, if they cannot question their parents and actively decide to obey, they are probably coerced into participating instead of giving their active consent and obedience. The assent process is not sufficient to insure children have a voice. Bluebond-Langner et al. (2005) give an account of the assent process that highlights how unnatural it is for children to be put through what amounts to a watered down consent process and to be forced to potentially break with mutual pretense to express an opinion. Bluebond-Langner et al. (2005) point out that children can be completely capable of understanding and making a decision but be unwilling to cause conflict in the parent-child relationship. To remedy the situation, Bluebond-Langner et al. (2005) describe a model of shuttle diplomacy where parents, children, and physicians have multiple discussions about prognosis and the research protocol without requiring a rigid assent process. They maintain that having the goal of a signed assent form too often means the process itself is a sham, as all parties may feel uncomfortable putting everything on the table during one penultimate meeting. If obedience is defined strictly by action and not by attitude, we might be able to say that children remain obedient. But, if we have a thicker concept of obedience, we will run into problems here. It is impossible for us to know whether children agree or not, so a focus on their behaviors over time might better help us see their perspectives.

Children in a phase 1 trial are unlikely to be carefree in part because they are so ill. But, a therapeutic misconception can mask fears and leave them with unanswered questions. The solution to anxiety is not to obfuscate or confuse children. Anxiety is best addressed through forthright conversations that reassure the child she is protected and loved. While dying children are likely to have unresolved fears, continuing on with treatment like nothing has changed may make the situation even scarier than it is. If children cannot be completely carefree, they should be the least anxious possible, and reducing anxiety requires forthright conversations.

Finally, continuing to battle cancer through enrollment in a phase 1 trial does not necessarily help children remain future-oriented. It may make children appear more future-oriented because they are still using language that suggests cure is possible. But, they are in fact not making preparations for their likely future. Some of what children do is to prepare for their future. What if that future is actually a premature death? Although it is difficult to contemplate, children deserve the chance to prepare for that possibility too. Preparing for death is not just about saying goodbye but also about how to live in the meantime. Preparing children for the future does not have to be morbid; it can actually mean deciding to enjoy the life one has left to live in preparation for the fact that one's life may be brief. It is also possible that with certain changes children might reasonably choose to participate in a clinical trial as a way of making future contributions. I will discuss these changes in the final chapter.

In the final analysis, it appears that parents cannot meet their obligations to a dying child by enrolling him in a phase 1 trial, at least not without significant changes to how phase 1 trials currently operate. Children cannot fulfill their social obligations because they cannot belie a true understanding of the situation. Therefore, enrolling in a phase 1 trial is in fact not a good moral decision, though parents should not be blamed in any way for their choice. There are larger

factors at work which we will explore in the final two chapters. But, enrollment in phase 1 trials cannot be justified with appeals to the parent-child relationship.

The Question of Family Autonomy and Hope in the Face of Death

I now turn to the strongest objection to my previous line of inquiry. Critics might argue that while parents may not objectively make a good decision by enrolling their child in a phase 1 trial the importance of family autonomy and the feeling of having exhausted every possible option outweigh the usual responsibilities and roles assigned to children and parents. In unusual circumstances, why not allow for unusual choices and outcomes? If these decisions were easy, they would not be the focus of a dissertation. Surely, the uniqueness of the situation might necessitate different actions than normal situations would. The important thing is for families to maintain hope, even if that hope comes at the expense of normal responsibilities and roles.

Clinicians often shy away from discussing prognosis, especially when it may be quite poor. There is a common belief that informing parents or children of their prognosis will rob them of hope and create undue emotional distress (Mack and Joffe, 2014). Clinicians also fear giving information that may prove in retrospect to be inaccurate. There can be a fear that patients and families will turn the knowledge of a poor prognosis into a self-fulfilling prophecy (Mack and Joffe, 2014). One way of avoiding prognostic disclosure is to continue giving families options, knowing those options probably will not work but can help maintain the family's hope. Although physician-researchers may provide disclaimers, giving the option of a clinical trial and expressing optimism is one way of providing hope. Here, I would respond that physicians speak as outside experts rather than family members. They both underestimate and at the same time overestimate their role in helping families maintain hope.

I say they underestimate their role by failing to appreciate that families may already suspect the truth and may actually want opportunities to discuss it. Psychological distress is high among parents caring for a child with advanced cancer, but prognostic information that is aligned with concrete care goals to reduce suffering helps to mitigate this distress (Rosenberg et al., 2013). Thus, distress is a natural part of having a seriously ill child, but it can actually be improved by helping parents acknowledge reality and then establish realistic goals. When interviewed, parents report feeling more hopeful and trusting the physician more if they receive a thorough explanation of their child's prognosis. A thorough explanation includes likely outcomes and also the encouragement to prepare for the worst. Physicians should present options for families to make end-of-life choices rather than focusing on clinical trials. In fact, a clinical trial should quite literally be an afterthought. Acknowledging prognostic uncertainty is important, but discussing the possibility of death can help parents set new, realistic goals that can be achieved. Similarly, children benefit from the opportunity to be heard and to voice their own concerns. In the final analysis, refusing to acknowledge a poor prognosis does not prevent resulting emotional pain. Losing a child is not any more difficult because families understand that the loss is possible (Mack and Joffe, 2014). Here, physicians often underestimate their ability to comfort through their honesty.

Dr. Dietrich Niethammer, a retired German pediatric hematologist-oncologist, has written about the need to be honest with seriously ill children and their parents. In his 2012 book *Speaking Honestly with Dying Children*, Niethammer maintains that a physician must tell the truth- even when that truth is difficult to hear. He writes:

> I am deeply convinced of the importance of truth. We as doctors cannot lie to sick children and adolescents, not even when we have bad news for them or when death is

> imminent. They must be able to rely on this honesty. It will also give truth value to our positive statements, something patients in these difficult situations desperately need. Evasive answers are lies too! (p. 8)

Here, Niethammer (2012) emphasizes that death is not alien to life. Death is part of every human being's existence. Failing to acknowledge death is dishonest; and one thing at the end of life is certain- parents and children ought to be able to confidently trust their physicians.

The physician's honesty can help shape a better care plan. Parents themselves do not see cure-directed and symptom-focused therapies as mutually exclusive. Integrative models that promote both are extremely helpful (Bluebond-Langner et al., 2007). At the same time, physicians who convey that prioritizing symptom-focused therapies really requires foregoing hope of clinically-significant improvement may dissuade parents from pursuing all of their options in the name of maintaining hope. It appears that the fear of pursuing or prioritizing symptom-focused therapies is not so much a matter of parents not wanting palliative care but of fearing a distressing reality. Combining the two approaches from the time of diagnosis would allow families to make a gradual transition rather than abruptly veering off in one direction. Parents need time to consider their child's deterioration and to accept palliation as true care. Prioritizing palliative care outcomes would necessarily mean only permitting minor risks and harms in service of a clinical trial. Focusing on quality of life truly does change the question from one of what risks to take for cure to what risks are permissible for others.

On the other hand, physicians sometimes overestimate their power in shaping a family's hope, as though families must and will always agree with how the physician sees things. It is wrong to believe that parents cannot maintain their own "economies of hope." In describing the

experiences of families waiting and preparing for a child's liver transplant, Knibbe and Verkerk (2009) point out that families take purposeful steps to change and manage their hopes during periods of transition. Their hope was both future-oriented and dependent on social context. Some parents focused exclusively on a desired outcome; others tried to prepare for all possible options to maximize the good. A third group simply lived day-to-day. Each way of hoping had potential pitfalls, but parents demonstrated their agency by negotiating their interactions with professionals on the basis of their preferred way of hoping. Hope is dynamic, and it is something mutually created by parents and professionals. It is not merely transmitted from one to the other.

Concluding Remarks

In this chapter, we have explored how the parent-child relationship changes in the face of serious illness and how and why parents and children enroll in phase 1 clinical trials. I argue that enrolling in phase 1 clinical trials, at least in their present form, is not a reasonable decision likely to allow parents to fulfill their responsibilities. I also argue that the social roles assigned to children conflict with the experiences children have in clinical trials. It is my contention that even the good motivation of maintaining hope is not a sufficient reason for enrolling children in early phase clinical trials. In the next chapter, I consider the nature of the physician's relationship to the parent and child in order to determine whether there is something about the practice of medicine that morally obligates physicians to encourage enrollment in early phase trials.

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Chapter Five

Physicians and Their Duties

In the previous chapters, we saw that families come with their own histories, values, and practices; and their unique attributes are often not appreciated by the medical profession. I argued that parents and children do not fulfill their major obligations and roles by enrolling in phase 1 clinical trials, at least as trials are currently presented and conducted. Now, I focus on the relationship between physicians and parents and children in order to see whether there might be a moral argument in favor of pediatric early phase clinical trials based on the physician-patient relationship. The medical profession itself has a history and deeply held collective values and commitments that need to be explored before we can fully understand the recent integration of scientific exploration and patient care. In this chapter, I first briefly examine the history of professionalism in medicine and the development of the concept of the pediatrician as a co-fiduciary of children's interests. Here, I point out differences between physicians who work with adults and those who work with children. I also consider how the unique history of pediatric oncology as a discipline has cemented a close relationship between science and practice. I then take up a discussion of the arguments often made in favor of physicians' involvement in clinical trials, questioning these arguments along the way. It is my contention that these arguments fail to provide a justification for enrolling seriously ill children in early phase clinical trials. Here, I look at the Jesse Gelsinger gene therapy case and consider both why events unfolded as they did and how this case study illustrates several fallacies about physician participation in early phase trials. Finally, I consider what it means to be a physician to a dying patient.

A Brief History of the Current Situation

Pediatricians have a unique responsibility to their patients. They are co-fiduciaries of children's interests with parents. All physicians are now considered to be fiduciaries of their patients' interests, though, for the adult patient, one of those very important interests is autonomy. But, the concept of fiduciary did not always play such a prominent role. Historically, medicine has constantly struggled with entrepreneurial self-interest versus selfless service to the sick. At the country's founding, medical services in the U.S. were market-based and contractual. Patients could choose from a variety of practitioners who promised certain results whether those results were in line with patients' larger interests or not. The contract limited physician duties to just those outcomes requested by patients. Medical ethics was nearly synonymous with the ethics of the marketplace- *caveat emptor* (McCullough, 2010, p. 12).

People did not generally trust physicians nor did society grant them deference or prestige. Interestingly, with the creation of infirmaries for the poor, physicians became skilled at withdrawing from cases when death was imminent as a way to avoid being blamed for the death (McCullough, 2010, p. 14). Physicians gradually became more accountable to the managers controlling the infirmary, and the practice of simply selling one's medical services on the open market became unsustainable. Contemporaneously, physicians began to have enormous power over their sick, institutionalized patients, and there were real concerns that they might experiment haphazardly on them. In response to the changing medical and social environment, John Gregory and Thomas Percival argued for medicine as a profession rather than a trade, pioneering the concept of physician as fiduciary (McCullough, 2010, p. 11).

John Gregory, a Scottish physician and moralist, condemned his fellow physicians' self-interested practices on the basis of David Hume's principle of sympathy (McCullough, 2010, p. 14). In accord with Humean sympathy, physicians should try to put themselves in the suffering patient's shoes and thus be motivated to cure and comfort. The primary purpose of medical practice was to serve the sick rather than to bring prestige or authority to individuals. A true profession required intellectual and moral standards (McCullough, 2010, p. 15). To this point, Gregory proposed two standards that would form the basis of a moral code for physicians as fiduciaries of patient interests. First, physicians would be expected to become and remain intellectually and clinically competent. Secondly, physicians should devote themselves primarily to the health-related interests of patients rather than to their own interests (McCullough, 2010, p. 16). Thomas Percival, an English physician, expanded Gregory's initial standards to include the idea that medicine was a public trust that should be preserved and passed on in the service of the sick (McCullough, 2010, p. 17). The notion of medicine as a public enterprise involving a collection of knowledge gave primacy to scientific processes by which a body of information can be refined over the years. The standards first articulated by Gregory and Percival remain the barometer for how well a physician acts as fiduciary even today.

While the concept of physician as fiduciary requires that physicians largely protect their patients' interests, one of the interests an adult patient has is to exercise his autonomy. Physicians may give their best medical recommendations only for the competent patient to reject their advice. The fiduciary standard then has far more to do with the physician's intent than with the actual outcome. So long as the physician makes recommendations, takes steps in the patient's interests, and solicits the patient's desires, he has fulfilled his duty. On the other hand, with children, the concept of the physician as co-fiduciary with parents requires balancing children's

own interests and desires as well as their parents' interests and desires. The pediatrician then has a special duty to protect the child that a physician treating an adult does not have to the same degree. We have high standards for those charged with protecting children, and the pediatrician serves in the unique role of co-fiduciary with parents (McCullough, 2010, pp. 17-8). It will never be enough then to take consent as a benchmark for an intervention. Consent or assent is important, but physicians have a professional obligation to protect the child's interests with or without her or her parent's consent or assent.

The special obligations pediatricians have to children "muddy" the proverbial waters when it comes to questions about children in research, especially in a pediatric sub-specialty like oncology that has been so successful in protecting and helping children who have cancer through a commitment to research. The history of pediatric oncology as a distinct discipline only began in 1948 with the observation by Dr. Sidney Farber that children suffering from acute lymphoblastic leukemia (ALL) had tumors responsive to folic acid. With this discovery, an era of innovation began resulting in the wide use of several chemotherapeutic regimens by the late 1960s (Pearson, 2002). Where children had only lived a few months previously, some experienced remission on the new medications. Children with ALL now have an 80% chance of long-term survival. The initial progress with leukemia has resulted in cures for other cancers as well. A full 70% of children diagnosed with cancer today will survive (Pearson, 2002).

Key to all of these fairly recent discoveries has been the combining of research and treatment to determine which regimens are most effective. Clinicians established the Acute Leukemia Group A in 1956 to share their discoveries, and this group has grown and joined with other cooperative networks to form today's Children's Oncology Group (Pearson, 2002). Multi-institutional collaboration has been the key to quickly finding therapies and comparing results.

The enormous success pediatric oncology has enjoyed comes from its whole-hearted embrace of a research culture. Paradoxically, a tolerant regulatory climate during pediatric oncology's early years allowed practitioners to innovate with few restrictions, and the success of their early discoveries has been used to make further research a standard part of therapy today (Unguru, 2011).

At the same time, there are concerns about the balance between providing clinical care and conducting research. Enormous success sometimes comes at the expense of current patients who may be randomized to what is eventually discovered to be sub-optimal treatment or who may bear the burdens of risky research for future generations. Pediatric physician-investigators report struggles with role conflicts. Research is seen as a necessity, and there is confusion with some study designs over what constitutes research and what constitutes standard therapy. But, these conflicts are often resolved with an appeal to the benefits of widely combining research and therapy (Dekking et al., 2015). As one interviewed pediatric physician-scientists working in Canada questioned, "I guess for me you know, in the morning I wake up and I say.... Am I more physician or more a researcher? Am I more a clinician or the other one?" (Czoli et al., 2011, p. 1).

By and large, pediatric oncologists reject the role of scientist and continue to embrace the role of therapist even when extensively engaged in clinical research (de Vries et al., 2011). They truly believe that research participation is likely in the best interests of individual patients, either because they believe that trials are at worst unlikely to be harmful and at best superior to receiving the same treatment in a clinical setting (de Vries et al., 2011). Physicians' therapeutic misconceptions allow them to operate in a dual role while still retaining the positive identity associated with caring for individual patients. Society gives rights and privileges to physicians

that it does not grant to scientists. Though scientific rhetoric might lead us to believe that physicians have theoretically embraced the necessity of truly scientific medical practice, they do not subsequently fully embrace the role of scientist. One Canadian pediatric physician-scientist summed it up, "I don't feel much... conflict between my role as a clinician and the researcher role because my primary role is a clinician and out of that... I'm acting also scientifically but I don't have the scientific questions prior to the clinical ones" (Czoli et al., 2011, p. 3). This position is termed "the similarity position" by Czoli et al. (2011). It is no wonder then that parents are understandably confused about the line between research and care and often view a phase 1 trial as an innovative new treatment rather than a controlled experiment to estimate appropriate dosages.

There are several mechanisms whereby physician-investigators prioritize their role as clinician. Boydell et al. (2012) conducted a narrative review of physician experiences, concluding that physicians use a reliance on regulations, denial, and self-reflexivity as management strategies. One way that physician-researchers tend to manage their dual roles is to rely on review boards and regulations rather than on their own judgment or insight. Although official research protections are obviously important, physician-scientists sometimes hide behind them to resolve their internal conflicts. They believe that if they follow the letter of the law they can manage any conflicts of interest without any personal critical thought or action (Boydell et al., 2012). For instance, in a narrative study, one physician said, "The world has evolved to a point that now in 2000's, these things are very strictly and well defined and I think it's very easy to not be in a position of conflict of interest and still do both things very well" (Boydell et al., 2012, p. 216). While some aspects of the research including data safety monitoring are best performed by outsiders, applying research ethics principles requires some individual judgment

and accountability. Failing to carefully consider each situation and simply relying on regulations can actually be a form of abrogating personal and professional responsibility. Some physicians also reported sending other staff in during consent conferences thereby keeping potential subjects at arms-length (Boydell et al., 2012). There seems to be a presumption in some cases that the research regulations developed by experts protect subjects, so there is no special need for the investigator to do more than follow these directives.

While some physicians try to reconcile their dual roles, others reported in the same narrative study that they occasionally resisted the combination. A few reported they would not participate on a research protocol that they did not feel was clinically in patients' best interests, though how they would determine this remains unknown. One said, "I wouldn't participate. I wouldn't have my patients participate in the study where I don't like the protocol and where I'm not very comfortable with the protocol irrespective of what the ethics say you know" (Boydell et al., 2012, p. 217). Others denied the pressure to perform research or simply did not promote studies to their own patients (Boydell et al., 2012). In a separate narrative study of Canadian pediatric physician-scientists, one explained:

> If there's a dilemma you go with the ethical side....The research has to take the back seat. I still have actually quite a lot of trouble with how the Tri- Council policies start and that is...something to the effect that everyone has a right to be in a research project. In other words, the way that it's painted is so positive. (Czoli et al., 2011, p. 4)

A third group of physicians reported that they managed conflicts by trying to critically reflect on their dual roles in new situations, though this reflection rarely produced specific

answers to challenges. They also sometimes sought the council of ethicists or colleagues. One physician commented:

> I think the most important thing for me is to . . . to maintain the critical thinking you know . . . not being completely, let's say, just devoted just to research or not being completely devoted to anything else but just always to critically analyze every single situation in which you are. That's the most important thing because that will prevent you from, you know, doing research that maybe finally turns out not to be ethical. (Boydell et al., 2012, p. 217)

Perhaps because they experience role conflict, physician-investigators usually see themselves as purveyors of information rather than co-participants during informed consent. Physicians-researchers maintain that their most important goal is to provide non-directive information so families can make their own decisions during the informed consent process (Simon et al., 2001; Yap et al., 2010). Physicians by and large do not see themselves as unduly influencing or making decisions for families (Yap et al., 2010). Yet, they also by and large believe that phase 1 trials benefit current patients. When asked to specifically respond either "Yes" or "No" to the question "Do you believe that current patients receive direct therapeutic/medical benefit from participation in phase 1 studies?" 60% of pediatric oncologists responded "Yes" (Yap et al., 2010, p. 3246). In an earlier study, an even greater 84% of interviewed physicians believed that pediatric patients received direct benefit from enrollment in clinical trials generally (Kodish et al., 1998).

The preceding paragraphs reveal that pediatric oncology as a specialty is unique in that it has advanced through a system of clinical research trials- a system most current physicians

support and view as necessary for continued advancement. At the same time, there are concerns about how to meet the obligations of fiduciary while conducting systematic investigations that may arbitrarily assign children to treatment groups. Most physicians resolve the conflict by maintaining that research and practice are similar, resisting the integration, or attempting to address moral issues as they arise in individual cases. But, there is substantial evidence that physicians are still conflicted about their dual roles. If physician-investigators themselves cannot clarify the distinction between their roles as researchers and as clinicians, we cannot expect patients to do so. Therefore, it is now time to turn to the dual questions of whether phase 1 trials really are just extensions of clinical care and if the need for research is compatible with simultaneously providing excellent clinical care. To answer, we must consider a series of arguments made by physicians and the medical profession generally in support of combining research and practice.

Unpacking Physicians' Arguments

In this section, I consider several arguments made about the combination of clinical trials and standard clinical care. These include the appeal to the indistinguishability of research and practice, the use of clinical equipoise to justify random assignment, the notion of physicians' scientific or intellectual duties and subsequent adoption of a utilitarian ethic valuing progress above most every other aim, and the failure to properly distinguish contractual versus covenantal medicine. I first consider whether research can properly be distinguished from clinical practice and explore the relationship between the two.

At the outset, a historical note is necessary. The research-practice distinction in bioethics was largely driven by the National Commission's deliberations. According to an analysis by

Beauchamp and Saghai (2012), the National Commission did not sharply distinguish between research and practice in their debates, though they did draw such a distinction in the Belmont Report. The National Commission encouraged additional oversight for clinical practice during their sessions, but they dropped the issue in the final analysis as a matter of prudent politics. The National Commission was in fact very concerned about physician innovation and the ill-defined boundaries of what constitutes standard clinical practice. But, members also recognized problems inherent in attempting to regulate both practice and research simultaneously. Had the members of the National Commission been unconstrained by the politics of the day they might have had sweeping things to say about medical practice as well as clinical research.

However, because of the distinction made in the opening sections of the Belmont Report, arguments against the distinction surfaced. At the very beginning of their report, Belmont's authors distinguished research from practice by defining practice as activities designed primarily to benefit individual patients and research as activities designed to systematically contribute to generalized knowledge. The research-practice distinction in Belmont is largely based on investigator intent (The National Commission, 1979). Dr. Norman Fost, a now Professor Emeritus of Pediatrics and Bioethics at the University of Wisconsin-Madison, published a comprehensive article articulating many salient objections to Belmont's research-practice distinction in 1998. In his article, Fost addresses five common claims made about research versus practice and rebuts each in turn while attempting to show that the two are not polar opposites. We will consider three of his arguments here. Although his examples come from the neonatal unit, his arguments are generalizable.

In one of his arguments, Fost (1998) questions the idea that an intervention is easily categorized as research or as part of clinical practice on the basis of the physician-investigator's

intentions (p. 226). If his intentions are to systematically investigate and advance generalizable knowledge, then he is engaging in research. As Fost explains, "As stated most pungently by Lietman [someone with whom Fost corresponded in the 1970s], as long as the physician promises not to learn anything from what he is doing, he does not need to submit his plan to the IRB" (Fost, 1998, p. 227). Or, as a Canadian pediatric physician-scientist expressed it:

> There's a conceptual level and there's the practical level. The conceptual level is I don't differentiate between my research and my clinical work so in other words the research questions that I ask in the studies that I conduct have direct implications to the clinical work. In fact, the research studies I've already conducted actually have changed the way I practiced. (Czoli et al., 2011, p. 3)

I agree with Fost that it is problematic to categorize intentions so strictly, but cases of overlap do not imply that there are no clear cases where research is obviously not practice. Fost admits that techniques like randomization often mean that a proposal constitutes research, but he argues that a better way of thinking about the distinction is to determine whether the investigator intends to collect information for the benefit of others. I would go a bit further here and argue that the distinction might also lay in the idea that in research a physician-investigator may do things that do not benefit the individual patient sitting before him in the service of future others. This seems a way to quite clearly distinguish research and practice.

Fost also argues against the idea that research is more tightly regulated than practice because it raises more serious ethical issues or is riskier than being a patient (1998, p. 228). Fost (1998) unequivocally recognizes that history suggests people have been abused and conscripted as research subjects, and these terrible historical incidents have understandably resulted in

regulatory changes and justifiable public backlash. Nonetheless, Foss points out that individual physicians have committed serious transgressions in the practice of medicine. He is obviously correct that individual physicians can behave heinously, but I think he underestimates the extent to which research for the "greater good" can be used to justify awful behavior and the lack of recourse mistreated research subjects have historically had. There is a particularly powerful rhetoric that research is a necessity, and its necessity can lead people to remain quiet in order to advance progress. Individuals who are mistreated as patients can file criminal or civil malpractice claims, and a physician can lose his license to practice and even go to jail. With current research regulations, investigators do face scrutiny, but we have seen historically and will see in the next case study that investigators have frequently gone on to high-profile careers after misconduct investigations.

Finally, Fost (1998, p. 229) questions the assumption that research means that physicians have more serious conflicts of interest than they might in clinical practice. He points out that the financial and career advancement incentives physicians have when participating in research could be comparable to those they face in fee-for-service or managed care systems. They could very well be tempted to perform unnecessary procedures or restrict care for financial reasons in clinical settings too. I think this is true, but I would argue that this means we need to increase our scrutiny of conflicts of interest overall. Research presents qualitatively different conflicts of interest compared to clinical practice, and the moral requirements of each are constructed in socially different ways. A physician acting clinically who sees a patient in clear need of certain medical interventions but who fails to provide them on the basis of padding his bottom line or one that prescribes unnecessary interventions to an unsuspecting patient has quite simply failed to discharge his duties as a physician. No reasonable person would suggest the physician's

conduct in these cases is praiseworthy. This conduct undoubtedly happens, but it should not happen. On the other hand, consider the research context. Imagine a case where a physician excludes a patient from a research protocol because he does not meet enrollment criteria or assigns a patient to receive a high dose of a potentially very toxic agent because the patient is one of the last enrolled on the protocol. This physician would not only be within his rights as an investigator to do so but might be praised as a scientist who is on the cutting edge.

Although Fost is examining research in general and not phase 1 trials in particular, I think the three previous arguments we have considered show just how different research and practice are. Especially in early phase contexts, they can indeed be separated. In the first case, while no one is suggesting that physicians should never learn anything from individual patients, a phase 1 protocol is focused on systematic discovery. The point of the phase 1 trial is to establish dosing guidelines with scientific precision, not to simply learn from those patients individual physicians happen to be treating. Additionally, intent does matter greatly in phase 1 contexts. An investigator may actually do things that hurt current patients, whether due to side effects from high dosages or failure to treat due to particularly low dosages given early in a protocol. These are done for scientific reasons, not for patient care. In the second case, being a patient in a phase 1 trial places the individual at significant risks she would not encounter in ordinary treatment. Physicians are certainly not responsible for outcomes in research in the same way they are during clinical care, as we will see in the case study near the end of this chapter. Finally, the role of researcher takes on almost mythical qualities in medicine today. The phase 1 investigator is not merely absolved from his customary obligations. He is seen as the hero- the potential conqueror of a vicious disease. Potential conflicts of interest are qualitatively different. While a physician might bow to external pressures in managed care, he would not have a moral imperative to do so.

For the phase 1 researcher, sacrificing some interests of today's patients is simply the cost of making medical progress.

Appealing to Equipoise

While I do not believe research and practice are truly indistinguishable or furthermore completely compatible, the argument regarding clinical equipoise perhaps has more potential. The basic argument from equipoise is that patients can be randomized to treatment arms when there is genuine disagreement or uncertainty about which treatment is better. A patient would reasonably consent to either treatment option since it is not known which one is preferable. Equipoise does not only or exclusively apply to individual investigators. Benjamin Freedman (1987) first introduced the concept of community clinical equipoise where equipoise requires that there be a genuine disagreement in the clinical community over treatment superiority. Individual physicians may have had differing experiences leading each to prefer one specific alternative, but collectively, the professional community may still be uncertain. Here, Freedman recognized that medicine was not merely a matter of personal preference but of community standards.

Yet, I believe that the most powerful argument against equipoise is that patients do actually have preferences about which physician treats them and which treatment is administered. Even when they sign a consent form, patients do not generally understand the need for random assignment and believe that physicians usually have some idea of the best treatment for their individual needs. A majority actually believed that assigning treatment by chance was immoral even when no one treatment was perceived as clearly superior (Robinson et al., 2005). Education about the need for randomization did little to change perceptions (Kerr et al., 2004).

Additionally, physicians themselves have individual treatment preferences and also make different choices on the basis of context. To maintain equipoise we must also remove a great deal of the art from medical practice. We cannot on the one hand emphasize the importance of the doctor-patient relationship or experiential wisdom and simultaneously assume patients ought not to have legitimate preferences in the research context. But, I find it hard to believe that patients or physicians really believe that their opinions and experiences do not matter- that treatment can really be assigned based on impersonal algorithms. But, equipoise requires just this type of practice to some degree. As an example, consider the SUPPORT study and its aftermath.

One need only look at the public outcry following revelations about the SUPPORT study to see that many members of the general public do not grasp the purpose and risks of research participation, even when physicians may have legitimate disagreements about what the standard of clinical care should be. Briefly, the SUPPORT study was a multi-site clinical trial that ran from 2003 to 2009. The study's purpose was to determine the optimal concentration of supplemental oxygen for severely premature infants. The study measured mortality and retinopathy to determine the best oxygen concentration. Clinical practice guidelines were to provide anywhere from 85%-95% oxygen, and physicians providing clinical care ostensibly used concentrations anywhere in that range. In the study, infants were randomly assigned to receive either 85%-89% oxygen or 91%-95% oxygen, and physicians were blinded to group assignment. Unfortunately, the data, evaluated after the study was complete, showed that infants assigned to the lower oxygen concentration had higher mortality rates. In 2013, the Office for Human Research Protections (OHRP) sent a letter to the lead study site at the University of Alabama-Birmingham informing researchers that they had violated informed consent standards because the consent documents did not specifically state a potentially increased risk of death or

retinopathy. At the same time, Kathleen Sebelius from the Department of Health and Human Services questioned the ethics of the research design (Hurley and Avrakotos, 2015).

Public Citizen, an advocacy group, released information about the SUPPORT study to the general public in April 2013 and sparked a national conversation about research ethics. A wide variety of physicians, other professionals, and lay people voiced their opinions with physicians, scientists, and even ethicists often arguing for the study and outsiders expressing concern about the risk to vulnerable infants. However, what was often missed or incompletely described was the foundational genesis of the conflict over SUPPORT. Even in cases where harms are not expected, research presents the possibility of risk from trial arm assignment, and parents usually do not accept increased risk or randomization just because they enroll in a clinical trial (Carvalho and Costa, 2013; Greenley et al., 2005). In one study, parents expressed disappointment when their child was assigned to the control group and actually continued to seek out the experimental therapy outside the trial, often disenrolling in search of a better option (Meinich Petersen et al., 2014). Parents expect physician-researchers to act like physicians and to provide individualized care, even though they might have signed a formal consent form specifying otherwise. The basic social argument from equipoise is that there was legitimate disagreement about optimal oxygen concentrations, and children could be assigned to various concentrations depending on institutional practice. Yet, I would argue that arguments from equipoise fail to consider how variable medical practice is and how important individualized care is to parents and patients. It is unlikely that physicians would choose an oxygen range by a flip of the coin without accounting for an infant's clinical condition. A physician would not refuse to increase oxygen if a child was not maintaining appropriate saturation or showed other risk factors, as might have occurred in the SUPPORT study where physicians did not know to which group an infant was assigned The

pulse oximeters were altered to show a predetermined oxygen concentration reading during the study to prevent investigator bias (SUPPORT Study Group, 2010).

When taken to the extreme, I question equipoise with a *reductio ad absurdum* argument by considering the case for mandatory participation in comparative effectiveness research. Relying on clinical equipoise, Orentlicher (2005) suggested that participation in low-risk comparative effectiveness research could be made a requirement for seeking the services of a particular physician. Since physicians themselves do not know which intervention is the best, there is no reason that people should not want to participate in a randomized research project. If the practice of medicine was simply the abstract weighing of probabilities, then this approach might be plausible. However, physicians routinely see medical practice as both an art and a science. Forcing patients to participate in research would neglect the importance of the physician-patient relationship. A doctor's job is not primarily to perform research in the clinic but to treat patients who present with medical needs.

Here, an illustration from another context is helpful. Imagine that a large health care system decided that two treatments appeared to be equal based on available evidence and wanted to sustain their relationship with both drug companies. They decided to randomly assign each patient one drug or the other. A physician would review the decision to make sure there were no medical contraindications (i.e. allergy to a major component, interactions with other medications, etc.), but there would be no substitutions on the basis of individual preference or patient circumstances. Here, I believe many patients and their physicians would consider the health care system overly intrusive in the doctor-patient relationship. Assigning a drug to patients randomly seems to take the art out of medicine, and a physician could reasonably prefer one drug over the other for an individual patient. It is unclear who should determine which reasons are good

enough to be exempt from randomization, but there are a variety of reasonable arguments that might not involve specific medical necessity (i.e. ease of access for the patient, administration timing, drug form, etc.). Aggregate data tells you something, but not everything, about the patient in front of you. Equipoise, then, is not a tidy concept in the research arena. If one would not accept random assignment to therapies thought to be effective outside research, what gives physicians the imperative to do so within a research framework that would require participation for medical treatment? If physicians have good reason to believe that their opinions matter in medical practice, then how can research, an arena where the physician's opinion decidedly does not matter, be substantially similar morally-speaking to medical practice?

We might assume that the phase 1 context is unique because treatment options have usually been exhausted before enrollment. There is perfect equipoise in that no one knows if a treatment works or if children will live any longer than they might have. But, it is important to remember the high failure rate of phase 1 agents here. It is unlikely that a drug will in fact have clinical benefit and eventually be approved for a certain indication. There is also the very real chance that the drug may make things worse. Here, I rely on aggregate data that suggests the relative ineffectiveness of phase 1 agents precisely because equipoise is purportedly communal. If equipoise is truly communal, then we must also remember that even if an agent benefits one patient it may prove ineffective in the final analysis. As an example, consider the Joshua Hardy case from 2014. Josh was a young boy with cancer who was suffering from a viral infection and was eventually given brincidofovir, an experimental drug that had shown early promise against the disease. The drug company's initial refusal to give Josh the drug resulted in public outcry and even death threats aimed at the company's executives (Cohen, 2014). Josh recovered from his infection thanks to brincidofovir. But, in late 2015, results from clinical trials showed that the

drug was not better than established treatments. It actually failed in a phase 3 trial even after passing through earlier phase trials. Patients seemed to get better initially but relapsed at high rates (Taylor, 2016). Even though Josh was helped, brincidofovir will not become the next big advance for cancer patients post-bone marrow transplant.

Other Arguments

There are two additional arguments to consider. First, there is the idea of physicians' intellectual duties and the need for pediatric research. Both of these fall under the broader concept of scientific necessity. This argument takes seriously the proposition that physicians have obligations to conduct research and advance medical practice for future patients. Expressed in another way, medicine requires research to advance. Therefore, scientific necessity dictates that it is sometimes necessary to put current patients at reasonable risk for the sake of future patients. This rationale is employed specifically in one federal category for pediatric research. A federal review panel can permit research that is more than minimal risk with no prospect of direct benefit and which would involve children with a specific disorder if it is likely to further understanding of said disorder. In these cases, studying the child's disorder or condition and therefore studying the child is a matter of scientific necessity (Roth-Cline and Nelson, 2014). Here, Roth-Cline and Nelson (2014) point out that most pediatric drug dosages are in fact extrapolated from adult data because there is frequently insufficient testing with children. This may be the case, but they do not make the necessary argument that children are in fact harmed from extrapolation. A great deal of information can be collected by extrapolation and gradually titrating doses for specific children. It remains to be seen whether every drug need be subjected to the clinical trial paradigm.

I have some sympathy for scientific necessity insofar as it distinguishes legitimate motivations (i.e. attempting to understand and cure) from more sinister ones (i.e. desiring simply to study an interesting process or deliberately causing disease). However, there are still difficulties here. Based on historical precedent and social perception, it is difficult to argue that participation in research is one of a physician's primary responsibilities or that it can justify the neglect of current patients' needs and interests. Hans Jonas' voice can be heard loudly here. There is a reason that physicians often do not identify as scientists. There is no doubt that they apply science and that they engage in deduction. Medical practice is scientific, but it is not research. And, it may be good that it is in fact not research. The physician provides care and comfort for the present, while scientists dream of the future. As Jonas writes:

> The destination of research is essentially melioristic. It does not serve the preservation of the existing good from which I profit myself and to which I am obligated. Unless the present state is intolerable [i.e. unsustainable, as in the case of an epidemic with many thousands of deaths], the melioristic goal is in a sense gratuitous, and not only from the vantage point of the present. Our descendants have a right to be left an unplundered planet; they do not have a right to new miracle cures…And generally, in the matter of progress, as humanity had no claim on a Newton, a Michelangelo, or a St. Francis to appear, and no right to the blessings of their unscheduled deeds, so progress, with all our methodical labor for it, cannot be budgeted in advance and its fruits received as a due. Its coming-about at all and its turning out for good (of which we can never be sure) must rather be regarded as something akin to grace. (pp. 230-31)

Finally, I consider whether the ability to obtain consent can justify research projects. Although I have previously suggested that consent cannot be a barometer for what constitutes

ethical research, I consider this idea because it is often used as a justification for parental acceptance of phase 1 trials. If parents wish to pursue phase 1 trials and take reasonable precautions, why should physicians be concerned? The federal regulations are particularly focused on informed consent, so it seems reasonable that consent is protective. With this argument, I urge readers to think about contractual versus covenantal medicine a la Ramsey.

To the argument from consent, I believe we would do well to consider whether informed consent is truly an act of autonomy or an act of authorization. Tronto (2009) argues that consent should not be viewed so much as an exercise of autonomy but rather as a transfer of authority. Physicians are given authority to act for a patient, and that power comes with concomitant responsibilities. Viewing consent as a patient exercising autonomy neglects the substantial power differences between patient and physician and requires physicians to merely discharge certain obligations without serving greater moral principles. Patients have no choice but to give physicians authority in many cases; this grant of authority is not so much an act of autonomy but an act of necessary self-preservation. Tronto (2009) reminds the reader that trust in medical professionals presumes that they will try to do as well as they can under challenging circumstances and not simply discharge a set of contractual obligations to meet minimum standards.

This characterization of consent as a grant of authority is particularly apt in the pediatric context. Parents are the primary fiduciaries of their children's interests, but they cannot meet many of their child's medical needs without professional assistance. They thus must grant some authority to physicians to make expert decisions about medical matters. Where adults can determine which medical treatment they want if any, parents are bound to seek necessary treatment out. Here, parents must presume that the pediatrician is trustworthy and that she will

protect the child's varied interests. Parents assign responsibility to those they believe will help them uphold their covenant with the sick child.

None of the preceding four arguments seem to me to justify physicians' participation in early phase clinical trials. One cannot argue from the doctor-patient relationship to justify clinical trials. While the relationship between physician and patient may not prohibit all research endeavors, it certainly is not a strong force in their favor. At the end of the day, clinical care and research care may only be combined ethically if research becomes more akin to clinical care or if research is completely separated from access to clinical care. We will explore how this might look in the final chapter.

A Case Study

Since I have been considering arguments made about research from the perspective of the physician, I turn now to a practical case to see how these arguments operate in the real world. The case of Jesse Gelsinger is one example of how early phase research can turn out and it is a very instructive one at that. The term "conflicts of interest" is often associated with physicians who have financial stakes in the success of research projects, but I argue that conflicts can run even deeper, as they did in Gelsinger's case.

Jesse Gelsinger, a newly 18-year-old young man who began contemplating trial enrollment before his birthday, died in 1999 during a gene transfer experiment conducted at the University of Pennsylvania (Steinbrook, 2008, Loc 5236/41798). While there had been concerns about safety, no one had yet died from a phase 1 gene therapy-related experiment (at least, not that had been reported publically). Jesse was born with ornithine transcarbamylase transferase (OTC) deficiency- a condition where the body cannot break down ammonia. Jesse was not

severely ill, but some patients can experience profound build ups of ammonia with life-threatening complications. Jesse's condition was controlled through adherence to a strict diet and multiple medications. So, although he claimed that he was participating solely to help infants who were dying of the disease, the promise of a fix and better future for himself was not far from his mind. He was referred to the trial by his own pediatric geneticist, Mark Batshaw- a co-investigator on the protocol. At the same time, Jesse was resolute, saying, "What's the worst that can happen to me? I die and it's for the babies" (Stolberg, 1999). Of course, Jesse and his family did not really expect him to die. They believed there might be some more minor risks, but the experiment was basically safe according to their understanding.

James Wilson, another co-investigator on the study in question, was a rising star in the gene therapy community by the time of Jesse Gelsinger's death. He was first attracted to the field of gene therapy when Dr. W. French Anderson performed the first in-human trial at the NIH in 1990, injecting a 4-year-old immune-deficient girl with genetically engineered white blood cells containing copies of the gene she was missing. Wilson admitted in a *New York Times* article that while in graduate school, "All I did was dream about gene therapy," (Stolberg, 1999). By the time Jesse died, Wilson was the director of the Institute for Gene Therapy at the University of Pennsylvania School of Medicine as well as the founder of Genovo- a company created to market and profit from his discoveries (Steinbrook, 2008, Loc 5271/41798). Wilson's involvement with Genovo had raised concerns at the university, but the company provided a substantial portion of his budget at the Institute. Wilson and university administrators seem to have believed that taking steps to reduce his managerial and scientific control, like preventing him from serving on the scientific advisory board, would help to mitigate any financial conflicts of interest (Steinbrook, 2008, Loc 5290/41798).

The study Jesse Gelsinger participated in was a trial of an advenovirus-derived vector containing a copy of the missing OTC gene. As a phase 1 trial, the goal was only to establish safe dosing levels for the vector. Groups of three or four participants were assigned to increasingly higher dosages (Steinbrook, 2008, Loc 5309/41798). Previous studies in monkeys had been concerning because several monkeys had died of a blood-clotting disorder and severe liver inflammation at high doses, but the dose in monkeys had been 20x higher than the highest planned in-human study dose (Stolberg, 1999). Jesse ended up assigned to the highest dose group in the trial, receiving his injection of the vector on Monday, September 13, 1999. Initially, he did well but developed complications on Monday evening. Over the course of a few days, Jesse experienced multi-organ system failure. By Friday morning of that week, he was declared brain dead, and his family made the decision to discontinue life support (Stolberg, 1999).

Jesse's death shocked investigators and his family. Initially, Paul Gelsinger, Jesse's father, maintained that his son had died well in the pursuit of society's greater good (Stolberg, 1999). However, after learning more about the trial, he wrote, "It wasn't until that three-day meeting that I discovered that there was never any efficacy in humans. I believed this was working based on my conversations with Mark Batshaw and that is why I defended Penn for so long (Steinbrook, 2008, Loc 5474/41798). In 2000, the family filed a civil suit which was settled out of court.

Wilson and his co-investigators, including Batshaw and surgeon Steven Raper (who delivered the vector infusion), were genuinely upset about Jesse's death; but Wilson, in particular, remained committed to the larger cause. He admitted to journalist Sheryl Gay Stolberg in a November 1999 article, "My concern is, I'm going to get timid, that I'll get risk averse." Raper vowed "to figure this thing out" (Stolberg, 1999) Batshaw was hit hardest. He

was after all Jesse's pediatrician. "What is the Hippocratic Oath?" he asked. "I did harm," he admitted (Stolberg, 1999).

Unfortunately, it later came to light that the investigators may have been a little too blithe about risks in the first place. Jesse should never have been involved in the study, as his liver was not functioning at the level required for inclusion in the study on the day he received the experimental medicine. Wilson and his co-investigators had failed to rigorously adhere to their submitted protocol and to notify the FDA of severe toxicities in other subjects. The investigators downplayed the likelihood of risks and failed to tell prospective participants about the deaths in non-human trials and the toxicities other subjects developed (Steinbrook, 2008, Loc 5406/41798). The university and the federal government conducted reviews of the trial and made changes to remedy the situation, and the Institute stopped conducting human trials. Genovo was sold to another company. Yet, even if there had been none of these missteps, it is unclear that Jesse or his family would have had a different outcome or felt any differently.

Jesse's death raised several issues, including the need for informed consent, the problematic nature of financial conflicts, the necessity of following the research protocol, and the need to report toxicities and stop potentially dangerous trials earlier (Steinbrook, 2008, Loc 5592/41798). Before the trial's approval, there were questions over whether babies with serious OTC deficiency should have been enrolled rather than adults with stable disease, since dying infants would have the most to gain if the experiment happened to work. It was decided not to enroll infants because they could not give informed consent in the face of potential danger. I tend to believe that the argument proffered against including infants was sound; I would have argued in favor of clinical innovation by individual physicians who could consider the individual

patient's context. Even if infants had been the subjects, I am not convinced that this fact alone would have changed public or professional outcry.

Unfortunately, the informed consent process largely failed in Jesse's case too. The consent form actually does mention the risk of death from liver inflammation but fails to disclose the fact that inflammation had actually been observed and implicated in the deaths of experimental animals. Liver inflammation was not a hypothetical possibility- it had been observed as a side effect already. The form also devoted much more space to discussing how risks would be mitigated than acknowledging the fact that they were indeed real (Wilson, R.F., 2010). Although James Wilson's monetary involvement certainly raised suspicions, it is difficult to see how it impacted the trial's outcome. Jesse still might have died even if Wilson had no vested interest in the trial's results. Information provision would have made the situation more transparent, but it may not have prevented a tragic outcome. Obviously, reporting earlier toxicities and citing the deaths in animals would have helped participants make a more informed decision or even resulted in the trial's suspension. But, all of these problems still do not remedy the underlying question. Why did Jesse and his father consent, recognize that there were inherent risks, and then act flabbergasted when those risks became reality? Why did the medical team seem shocked their phase 1 trial went wrong? We have already discussed how most investigational agents will never make it to a phase 2 trial, and everyone acknowledges there is risk when an agent has never been tested in humans. Why the shock in Jesse's case? Obviously, everyone involved was saddened by Jesse's tragic death; however, an unfortunate outcome in a first-in-human experiment cannot conceptually, at least, be implausible?

James Wilson published an editorial on the lessons he learned in 2009, but this piece too leaves me wondering if he really learned anything much at all. Though obviously a somewhat

defensive move to tell his own story, Wilson's lessons (2009) include the need to follow the trial protocol to the letter because it is a contract with patients and regulators, the imperative to report any information that causes you to debate whether it should be reported, the difficulty of managing real or perceived financial conflicts of interest, and the realization that informed consent requires objective third-party involvement. All of these observations are accurate, but I believe they fail to account for the underlying reasons why Jesse's death sparked such national concern.

In my view, Jesse's death sparked concerns precisely because society does not generally accept physicians' arguments about involvement in research. We have a romanticized view of just how promising new treatments are, believing that physicians are far more sure of the positive effects than they actually are. Physicians' more nuanced arguments about research are discussed in professional contexts, but they are usually not shared directly with patients. Some physicians operate from an overly optimistic position as well. Hence, the misinformation and confusion we see here.

First, let us consider the research-practice distinction. It is clear that this was a research project and everyone acknowledged that fact to a point. But, Jesse's father, and perhaps Jesse too, believed that gene therapy had been working- that it had been at least somewhat successful for people clinically. There was a real belief, which was certainly not substantiated by the evidence base, that gene therapy was bound to eventually work. The fact that Jesse's own treating physician recommended the clinical trial to him made the research seem like part of the clinical process. Jesse verbalized a recognition that his enrollment was different than being on treatment, but he still hoped the protocol would eventually change his current treatment regimen (a huge number of pills taken every day) when the truth was even in ideal circumstances Jesse

may not have been a good candidate for gene therapy by the time it truly advanced. It would likely have been years before current patients saw any benefit.

Secondly, let us consider the idea of equipoise here. Equipoise may not appear to be a significant factor here, but it truly was. Jesse's current regimen was burdensome yet had kept him healthy. He would have liked an easier treatment regimen and believed gene therapy might definitively cure him, eliminating the daily burdens he faced. Intuitively, Jesse believed that the trial offered a clinically acceptable option. The physicians involved would have considered equipoise differently. For them, the fact that there was no definitive cure and the available regimens not always successful meant that gene therapy had promise. Equipoise might have been more readily applicable in the context of dying infants, but performing a risky experiment with dying infants came with its own set of problems. Still, in this case, researchers had wed themselves so closely to gene therapy that they could barely see the proverbial "forest for the trees." While equipoise might have been invoked, everyone involved felt gene therapy would be the next big breakthrough.

The physicians clearly felt they had scientific obligations, as Wilson, at least, continues on with other projects even after Jesse's terrible outcome. Yet, this case gives a particularly compelling example of how incommensurable science and medicine actually are at times. The investigators, as good scientists, should have followed the trial protocol to the letter. They should have tracked and immediately reported adverse outcomes as a matter of scientific accuracy. A good scientist knows that data collection is a matter of fundamental integrity. Perhaps, Wilson and his colleagues simply overlooked these things or made simple errors. It is possible. But, I would argue that they also may have, possibly even subconsciously, confused clinical discretion and scientific precision. Since they were truly committed to the project and believed the vector

would work, they might have neglected to report outcomes that would have prematurely ended the trial. If the medical situation was not extreme, these physician-scientists may have felt they could control the situation and still get the scientific data they needed. The investigators appeared to have scientific obligations when they wanted them and claimed clinical discretion when they did not. James Wilson's article basically showed that he learned he really was a scientist when performing early phase research, and he did not have the clinical freedom he had otherwise.

It is apparent when Jesse's father speaks that he believed physicians retained their covenantal roles with Jesse- that they would watch out for his son and make sure things were not too dangerous or harmful. Batshaw's response to Jesse's death showed that he really did recognize how he had failed to protect a patient- how he had done harm. The other investigators appeared less affected, and it may be because they were not Jesse's physicians before the trial. They viewed their relationship with subjects as contractual. But, the real question, which will probably never be answered, is why Jesse's father and possibly other subjects believed that investigators were in a covenantal relationship with them? Here, we must remember that covenant is distinguished from contract through purity of intention. How likely would ill teens and their parents have been to enroll if they truly believed the investigators had interests which might supersede their clinical welfare? I do not know the answer. But, I imagine that recruitment would have been a much more difficult task, and Jesse might still be alive.

Caring for the Dying Child and Her Family

Giving up the notion of phase 1 trials as treatment options is difficult precisely because it requires us to consider what physicians should do when caring for dying patients. As Matthew

Miller (2000), a physician-researcher who served as a fellow at the Dana-Farber Cancer Institute explains:

> At some point during our initial encounter, most patients would turn to me and say something to the effect that having a small chance of responding to an untested agent is better than having no chance. Whether this was uttered as an entreaty seeking confirmation or as an invocation warding off further discussion was often difficult to know. In either case, it was, for me, a harbinger of discomfort and signaled a critical juncture in my relationship with a patient. At this point the conversation veered in one of two radically different directions: toward a hopeful and almost always short-lived intermission from despair, or toward a final and often desperate reckoning with the likelihood of a looming death. (p. 36)

I now consider how physicians and patients can truly have hope in the midst of suffering without relying on the myth of the phase 1 trial. It is my contention that caring for patients, especially children, at the end of life requires physicians themselves to answer questions about their own life's meaning.

The need to see or create meaning amidst suffering is not a new idea. One of the most famous physicians to write about the human condition and the search for meaning was Viktor Frankl. Frankl, a psychiatrist, psychotherapist, and philosopher, survived for three years in Nazi concentration camps and then went on to develop a particular kind of existential analysis that he termed "logotherapy" (Frankl, 2006). Frankl (2006) described man's ultimate motivation as a search for meaning in life. As he described, "This meaning is unique and specific in that it must and can be fulfilled by him [a person] alone; only then does it achieve a significance which will

satisfy his own will to meaning" (p. 99). Especially when surrounded by death and suffering, as one might experience when caring for very ill children, there is a human need to find meaning in the situation and then to be able to take action to make that abstract meaning a concrete reality.

Frankl (2006) contended that man answers questions about his life's meaning through his responses to the problems it presents and how he responds. "Ultimately, man should not ask what the meaning of his life is, but rather he must recognize that it is he who is asked. In a word, each man is questioned by life; and he can only answer to life by answering for his own life…" (p. 109). Thus, it is necessary for each person to make as free as possible a choice about what his life will come to represent. We cannot be in the business of assigning meanings to other people's lives on the basis of what we feel they can or should do for others. The true way of giving meaning is to provide a space in which people create their own meanings and paths to their own fulfillment. Some people may willingly take on an identity rooted in sacrifice, but not everyone can be expected to do so. The physician who takes the courageous step of recognizing death's inevitability and allowing parents and children to talk openly is one who allows families to find their own meaning. The phase 1 trial can only give temporary meaning; it can never give the kind of clarification or resolution we want when faced with death. Maintaining false hope often means foregoing the opportunity to discover the real meaning in personal tragedy.

Research provides a way of finding future meaning in spite of the suffering of current patients. The promise that "things will be better in the future" sustains health care providers when they feel helpless to do anything else for a dying child. After all, if survival rates or quality of life do not improve, where is the hope? Here, I would give the answer that there is hope created by journeying with a patient- by guiding their passage from this life to the next.

Physicians create their own meaning by what they do for today's patients. When death comes, there is power and hope that comes from making it the least terrible it can be.

One could also question what possible meaning a family could find during a child's illness besides the quest for cure. The problem with this line of inquiry is that it fails to account for the unlikelihood of the search's success. The focus when enrolling in an early phase trial is changing the end result. But, just as important, Frankl (2006) reminds us, "When we are no longer able to change a situation- just think of an incurable disease such as inoperable cancer- we are challenged to change ourselves" (p.112). Changing themselves- their goals, hopes, and dreams- is perhaps the bravest decision parents can make. Changing allows them to determine what life is asking of them now as the parents of dying children.

Concluding Remarks

In this chapter, I have explored the duties and responsibilities assigned to physicians at different times in history, considered various arguments about physician's participation in clinical research, and examined how they play out in a real phase 1 setting. I also considered the idea that phase 1 trials can never give the kind of hope that is needed. If death requires changing oneself, then relying on the myth of the phase 1 trial as potential savior is only more damaging when it prohibits a change in goals. Having now considered arguments made about parents, children, and physicians in phase 1 clinical trials, it is my contention that in their present form they do not allow players to meet their relational obligations or to maintain their social roles. In the next chapter, I explore how phase 1 trials might be modified in order to address the concerns laid out in previous chapters.

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Chapter Six

Moving Toward Better Alternatives

In the previous chapters, I considered various arguments made in favor of permitting parents, children, and physicians to participate in the current phase 1 trial system. It is my contention that the present federal regulations leave a good many questions about children in research unanswered, and appeals to various relational or scientific obligations cannot truly justify phase 1 trials as they are generally conducted. Therefore, in this chapter, I explore whether phase 1 trials could be modified to make them more ethically acceptable. That is, is there a way to generate the type of benefits we first considered in the *Introduction* (i.e. increased survival from gene therapy) while remedying the ethical problems we have subsequently discussed? My analysis here is not meant to be comprehensive; rather, it is designed to provide fodder for more extensive thought. Here, I will make the case for a clinical innovation paradigm. Inherent in this discussion is the need to define palliative care as standard care at the end of life. Then, I consider potential criticisms and end with a final review of my thesis.

To my mind, there is at least one promising way we might accomplish the goal of rendering early phase clinical trials more ethically acceptable. We could make clinical trials more truly like clinical care, allowing physicians and families to fulfill their obligations without relying on therapeutic misconception. This would require early phase trials to resemble clinical innovation and physicians to fulfill all of their patient care obligations. This potential solution seems the most promising to me, as it allows for individualized patient care while still permitting medical innovation. Clinical innovation has always been a part of medicine, and it has resulted in many helpful interventions without the use of the standard RCT paradigm (i.e. many surgical procedures, interventions developed before the advent of RCTs, etc.).

A Note on Terminology

In the present project, I have not made a rigorous effort to separate palliative care from hospice care. I take them to be virtually synonymous at the end of life and so use them interchangeably. At the same time, it is important to note that palliative care can and should be employed throughout the course of a serious illness to mitigate impacts on quality of life; hospice care is a unique form of palliation appropriate at the end of life, generally defined as a life expectancy of six months or less. Hospice care includes a spectrum of medical, psychological, spiritual, and practical interventions provided in many locations, including at home, in free-standing facilities, or in hospitals. Many physicians feel comfortable providing symptom-focused care as well as curative care, but there are additional challenges as patients worsen. A dedicated pediatric palliative medicine and hospice service can provide both short-term treatment to those who are not terminally ill and comprehensive end of life care.

Palliative Care as Standard Care

From the outset, it is important to examine the role palliative care should play at the end of life and consider whether it could in fact be considered standard care. Palliative care as standard care is a construct we will rely on in all proposed solutions. Reframing the discussion by defining palliative care as standard care is essential because the argument made in pediatric oncology is that clinical trials are actually the standard of care. First, it is important to define standard of care and to consider how defining treatment as standard care changes medical practice. What constitutes standard care has historically been associated with malpractice suits and based on expert witness testimony (Moffett and Moore, 2011). Physicians themselves also establish clinical practice guidelines that can serve as de facto standards of care. It is not my

intent here to use a legal definition of standard of care primarily because a legal definition requires physicians to provide only minimally competent care. The law does not require medical excellence; but I believe physicians should as a matter of ethics strive for excellence (and most want to provide excellent care rather than doing only what is minimally required to avoid a lawsuit). So, I use the notion of clinical consensus or guidelines here as the definition for standard of care.

I do not believe any reasonable person would argue against palliative care on a principled basis. No one wants seriously ill patients to suffer. Why then do we need to actually define hospice and palliative care as standard care at the end of life? The answer is precisely that everyone believes palliative care is good practice, yet implementation remains staggeringly variable. While everyone agrees it is a good idea, our beliefs and our actions do not match. Too often pediatric hospice care is an afterthought rather than an integral part of treatment.

This is probably in part because pediatric oncologists report discomfort when caring for dying children and a lack of training. Targeted pediatric hospice services are frequently not available (Hilden et al., 2001). A large-scale survey of pediatric oncologists found that few have access to inpatient palliative care services even though more than half of their patients die in the hospital. When hospices refuse to take children who are receiving any form of chemotherapy, referral is particularly low (Fowler et al., 2006). Palliative programs are also frequently at the mercy of hospital funding, as they do not bring in substantial outside funds (Feudtner et al., 2013).

Unfortunately, physicians also often do not refer children in time for them to reap substantial benefits even when there is easy access to comprehensive services (Twamely et al.,

2014). In one retrospective review of cases in the United Kingdom, a country with a longer history of providing comprehensive hospice services for children compared to the United States, there was no end-of-life care plan in 25% of cases, and families were not given a choice about location of care or location of death in approximately half of the cases (Heckford and Barringer, 2014). This finding may be in part because there is still little agreement about when to initiate a referral to palliative and hospice care among pediatricians (Thompson et al., 2009). One study of North Carolina hospice programs found that lack of pediatric-specific clinical services and inconsistent care plans between pediatricians and hospice providers were the most common barrier when providing pediatric end-of-life care (Varela et al., 2012). Part of the confusion may stem from the fact that hospice care should be employed when a patient is expected to live six months or less, not only when they are likely to die very soon.

Despite these disagreements, calls for a greater emphasis on pediatric hospice care for children suffering from advanced cancer are increasingly frequent. In 2004, Ulrich et al. suggested that palliative care may be a useful adjunct to phase 1 trials. Both endeavors seek the best outcomes for children, and their combination would allow children to receive maximum benefit. Although there remain concerns about how palliative care might be integrated in trials, the American Academy of Pediatrics called for integration in 2000 (Ulrich et al., 2004). In a very recent article, Weaver et al. (2015) suggested standards for pediatric hospice care and argued in favor of making pediatric palliative care a standard of care for all pediatric oncology patients. Making pediatric hospice and palliative care standard and customary care would make it more widely available and acceptable. It would no longer simply be a nice idea; it would be a necessity.

Even when hospice is desired, choosing it may prove harder than foregoing it. Consider the case of Julianna Snow, a five-year-old suffering from neurodegenerative Charcot-Marie-Tooth disease. Snow's mother is a neurologist, and after putting her daughter through several years of treatment and repeated hospitalization, she inquired whether Julianna wanted to be admitted if she were to get very sick again. Julianna was clear that she would rather die and go to heaven than have to endure another painful admission. After considering Julianna's medical reality and the fact her condition is terminal, Dr. Snow allowed her daughter to choose home over the hospital. If Julianna worsens, she will be kept comfortable and allowed to die in peace. The family's decision drew praise and controversy with physicians and bioethicists expressing divergent opinions (Cohen, 2015). Even with a mother who is a physician, many people felt Julianna's parents were giving up on her, and what parent wants to be perceived as giving up on their child?

In my opinion, making palliative care a standard of care is crucial because it fundamentally changes how we view it. When someone refuses a standard intervention, physicians ask questions to make sure the competent patient understands or decision-makers appreciate the necessity of treatment. Parents who reject standard interventions are scrutinized especially closely. Their decisions sometimes prevail, but there is a general presumption that they should seek out standard medical care on behalf of their children. With standard care, there is a presumption in favor of it unless there are exceptional circumstances. The fact that we presume in favor of standard care presents a problem for arguing that research is really standard care. It is difficult to claim an intervention is standard when we need to study it to determine whether it is in fact beneficial. Explaining that palliative care is standard care helps all patients understand their participation in a clinical trial should be motivated from altruism, as research is

about improving future care (Grünwald, 2007). Hopefully, patients will then also feel free to advocate for services that improve their own quality of life.

In order to establish pediatric palliative and hospice care as standard care, we need to examine whether children's medical and psychosocial needs and their parents' needs are adequately met and decide if hospice might be able to remedy some deficits. Overall, many children appear to suffer at least some distressing symptoms without adequate relief at the end of life. Retrospective interviews with parents revealed that most children suffered at least one disturbing symptom in the last month of life with continuing aggressive cancer treatment, and successful relief was achieved in only one quarter of those patients (Wolfe et al., 2000). Children who continue to receive cancer-directed therapy suffer more burdensome symptoms in the final month of life than children who receive palliative care only (Heath et al. 2010), and those with advanced cancer primarily identify pain, fatigue, drowsiness, and irritability, indicating these symptoms cause them high distress (Wolfe et al., 2015). Emotionally, anxiety is a symptom many children experience at the end of life and one that remains largely unmitigated (Hechler et al., 2008).

Parents also experience distress when their children are fearful or in pain, though they have conflicting views about aggressive treatment at the end of life. In one retrospective study, parents rated the decision to continue chemotherapy at the end of life negatively (Hechler et al., 2008). In another survey of bereaved parents, most whose children had continued to receive cancer-directed therapy after they recognized a cure was not possible reported that their child had suffered from treatment. Yet, more than two-thirds of parents would still recommend either standard or experimental chemotherapy to other parents of children with advanced cancer in order to control symptoms or extend life (A small percent cited cure.), though the perception of

their child suffering did decrease the likelihood of the recommendation (Mack et al., 2008). Parents appear to benefit substantially after a child's death if they believe their child did not suffer. McCarthy et al. (2010) found that time since death, parental perception of the oncologist's care, parental perception of their child's quality of life during the last month, preparedness for the child's death, and financial hardship all impacted parental grief. Furthermore, if a child's pain and other symptoms cannot be controlled, parents suffer more severe continuing distress even four to nine years after their child's death compared to parents of children who receive appropriate symptomatic control (Kreicbergs et al., 2005).

Clinicians themselves report positive outcomes when children receive hospice care. When interviewed in 2005, medical providers at Helen Devos Children's Hospital in Grand Rapids, MI overwhelmingly preferred hospice support during the dying process, specifically mentioning meeting non-medical needs and the location of death as benefits (Dickens, 2010). A retrospective analysis of pediatric hospice deaths at one institution with a pediatric hospice program between 2006 and 2010 found that 73% died at home or in a hospice unit and 18% died on an oncology unit. Only 6% of children died in the intensive care unit, and 2% died in the emergency room (Thienprayoon, 2015). This finding suggests that children are able to be supported in the least restrictive medical environment when they receive hospice services. Based on the fact that children and their parents suffer at the end of life and physicians recognize the positive impact hospice care has, I argue it is apparent palliative care should be standard care. I now examine whether research participation could be combined with palliative care in some way to mitigate ethical concerns.

Making Clinical Trials More Clinically-Oriented

Let us now turn to a way of making early phase trials more ethically acceptable. Replacing standard protocol-based trials with a clinical innovation paradigm would allow physicians to provide personalized care while also trying new interventions they hope will benefit the patient in front of them, so long as palliative care goals could simultaneously be met. Clinical innovation is already a dominant paradigm in surgical specialties, as it is extremely difficult to conduct an RCT when outcomes depend on individual surgical skill and comfort. Physicians do what they think is best based on individual clinical circumstances, and informed consent resembles consent for a normal clinical procedure. For instance, treatment for pediatric hypoplastic left heart syndrome, a condition where the main pumping chamber of the heart is undersized and unable to supply the rest of the body with adequate blood flow, has evolved due to innovative procedures performed by individual surgeons. Surgical intervention developed from necessity and required individual surgeons to try different techniques in the hopes of helping their patients. Both the Norwood palliative procedures and heart transplantation are now treatment options, and the preferred option varies depending on hospital and surgeon preference. Although little data is available regarding long-term quality of life, many children have survived both surgeries and enjoyed significantly longer lives than they could hope for without intervention (Flanagan-Klygis and Frader, 2005).

In order to bring the ethical issues into focus, I now am going to describe a specific experimental case for review. In April 2013, Hannah Warren, a young South Korean girl suffering from tracheal agenesis, was admitted to a Peoria, IL hospital for experimental treatment. She received a trachea constructed from her own stem cells. Warren's cells were allowed to grow on a plastic lattice and the pseudo-trachea was then implanted. The FDA

approved the procedure under a compassionate use protocol, and the host hospital covered the surgeon's expenses. Warren had never been able to leave the hospital in the nearly three years since her birth, was unable to eat, swallow, or breathe on her own, and would soon die without intervention (Fountain, 2010). Unfortunately, while the new trachea worked well for several months, Hannah had lung complications, needed a second operation, and finally passed away in July of 2013 (Wilson, 2013).

What was the difference between the experimental care Hannah Warren received and the care rendered in phase 1 trials? In both cases, the outcomes are uncertain. However, in Hannah's case, the physician performed a unique procedure designed to be therapeutic for her. The entire process was still experimental in that it had not been tried in a child previously, but every effort was made to insure her survival specifically. Contrast this state of affairs with a phase 1 trial. In a phase 1 trial, the investigators are concerned with aggregate rather than individual results. Success is defined by what we learn for future phases in terms of optimal dosages or techniques. Dr. Macchiarini claims to have learned a great deal from Hannah’s operation, but he was still providing personalized care. Macchiarini has performed several other operations on patients, and some have survived for several years. He has followed their courses and learned more about regenerative medicine while continuing to treat individuals. When Hannah began to decompensate, she received all of the medical and psychosocial care doctors and her family deemed fit. There was no exclusion from certain types of care for eligibility or practical reasons, as there might be in a phase 1 trial. Phase 1 trials often have specific starting and stopping rules, eligibility criteria, and rules about what outside care can be provided. In clinical innovation, patients are given the kind of treatment they need rather than the care dictated by a standard protocol.

The type of experimental therapy Hannah Warren received seems ethically defensible. Hannah was going to die without some type of tracheal replacement. Her parents felt that her best chance for success was through a stem cell transplant. Hannah had very limited quality of life and would never leave the hospital in her current state. No transplant procedure existed, so a highly specialized treatment regimen had to be developed. Hannah received all available care to insure her surgery was a success, and her quality of life did not seem to be much worse post-operatively. Multiple media outlets reported she was able to receive her first licks of food by mouth, and she appeared smiling in multiple post-operative photos. While the outcome was uncertain at best and improbable at worst, the physicians caring for Hannah saw her as a patient rather than a research subject. They were her physicians first, and any useful information they discovered was a bonus in addition to the satisfaction of trying to save a young girl's life.

There have already been calls for more individualized innovation in pediatric oncology. A move toward individually targeted therapy is promising because it would take tumor molecular characteristics into account. Since conventional chemotherapy is already quite effective, targeted therapy necessarily involves a very small group of heterogeneous patients (Mussai et al., 2014). These children may have unique tumor genetic markers or biochemical factors that are responsive to certain medications in the laboratory. Targeted therapy allows for faster dose escalation and early clinical outcomes because it uses individual biomarkers and leverages tumor vulnerabilities (Hirsch et al., 2015). Targeted therapy can create therapeutic advantage very early in the development process (Kearns and Morland, 2014). Since rare biological profiles would require an innovation paradigm rather than large-scale clinical trials, improving survival rates might very well eventually require a clinical innovation paradigm.

Of course, clinical innovation is not without its ethical complications. With no protocol to dictate what data is collected and which outcomes are considered significant, it is difficult to determine when innovative therapies actually become standard care or to compare results. With the help of epidemiologists and statisticians, this may not be an insurmountable problem. Parents also do not have the opportunity to hear a full explanation when physicians have limited understanding of an intervention, threatening their ability to meaningfully exercise decision-making capabilities (Reitsma, 2010). Additionally, customarily accepted, untested therapies sometimes demonstrate an unacceptable risk-benefit ratio in the long-run. Physicians cannot give parents information about long-term outcomes that they do not in fact have. It is always possible that individual experimentation can be reckless and result in mixed future outcomes (Reitsma, 2010). But, perhaps the largest problem with innovation is that there is no separation between clinical care and research, leading physicians to possibly underestimate risks and parents to think there is actually evidence behind a given intervention. Here, maintaining a focus on palliative care as standard care is crucial. Even within clinical innovation, physicians still must decide if experimental interventions are overly burdensome.

Critics might allege that my proposal to rely on a clinical innovation paradigm still does not solve the issue of infrequent use of hospice services or that children in fact do not have worse end-of-life experiences when they participate in research as it is currently conducted. To the first argument, I would reply that physicians do need to be more mindful of palliative care, and policymakers and ethicists should call physicians to their clinical responsibilities. Establishing palliative care as standard care means that it is no longer a nice, optional idea. Where there is substantial evidence that palliative and hospice care makes a difference, it should be employed. This is really a matter of clinical competence. Clinical innovation requires the provision of all

necessary medical care, including palliative and hospice care. There will be occasions where physicians will be unable to offer innovative interventions because the child patient's quality of life and function are so poor. Additionally, responsible physicians are morally required not to provide futile or overly burdensome treatment. They should encourage patients to choose hospice in these cases, and they should encourage parents to seek palliative care from the very beginning of their child's illness. I would hope that taking total clinical responsibility for a patient would naturally lead to an increased use of services that might make that patient's life better.

The second counterargument about end-of-life outcomes not being worse among phase 1 trial participants is particularly interesting. Perhaps paradoxically, one argument made in favor of enrolling in phase 1 trials and/or pursuing aggressive therapy at the end of life is that children do not in fact have worse end-of-life outcomes when they enroll in trials. Levine et al. (2015) did not find any significant difference in end-of-life outcomes between those who chose phase 1 trial enrollment and those who did not enroll. Variables included number of end-of-life conversations, timing of conversations, hospice enrollment, hospice length-of-stay, and a decision to forego life-sustaining technology. Yet, I would argue that there is a hidden variable here- the fact that we do not deal well with children who are dying overall. The fact that children in phase 1 trials do not do any worse is a very low standard to set. All children should have access to comprehensive palliative care, and they should not have to suffer for the sake of others at the end of their lives. The moral issue then is not just a matter of phase 1 trial participants having similar access to other children but of all children having suitable access. Not to mention, numerical outcomes are only one aspect of hospice care. The quality of a child's life and family

experiences cannot always be neatly captured via survey. Clinical innovation allows physicians to try new therapies while also meeting children's individual palliative care needs.

One might also wonder if there is a way to make palliative care part of phase 1 trials without complete separation. However, there are potential ethical pitfalls in making palliative care a standardized part of phase 1 trials, including the possibility that it could become an undue inducement for participants if better end-of-life care is available within phase 1 trials than outside of them (Kapo and Casarett, 2002). Relying on a clinical innovation paradigm is crucial because the needs of each individual child and family are different. True palliative care will never look the same for each individual child and neither should the care they actually receive.

Evaluating Clinical Innovation

The real test for a clinical innovation paradigm is whether it can address some of the objections to phase 1 studies I initially raised in earlier chapters. Clinical innovation certainly decreases concerns about the exploitation of patient-subjects since patients remain just patients, and physicians act as clinical care providers. Paul Ramsey would likely be very happy, since children would not be used in the experimental service of others. Here, I leave open the possibility that once evidence gradually amasses from individual cases it may be possible to conduct later phase clinical trials. Researchers would need to "sin bravely" a la Ramsey in these cases, but such actions would occur much later in the development process. What this might look like is a topic for another paper, but I raise the issue here merely as a nod to future directions for ethics research.

Relationally, clinical innovation allows parents and children to maintain their normal roles and responsibilities when illness strikes, while physicians can continue to provide

personalized care. Of course, clinical innovation relies heavily on all parties discharging their roles and responsibilities, but this is really the case whenever families and physicians come together for the sake of a child. Physicians must consider innovative procedures within the context of palliative and hospice care. Uncomfortable discussions about end of life care will have to occur, or families may not have any more opportunities to prepare for a child's death than they do now. However, a clinical innovation paradigm requires physicians to follow standards of care, including standards for end-of-life care. Failing to do so is really a failure to provide competent medical care. Since most physicians very much want to provide excellent care, the recognition of palliative care as standard care is a much better incentive to incorporate it into practice than any set of regulations can provide.

Final Remarks

In this dissertation, I have considered whether phase 1 trials as they are currently conducted can be justified from a regulatory perspective or from a relational perspective. My analysis has found that they cannot generally be justified from either perspective. As they are currently conducted, phase 1 trials rely on a tenuous hope of benefit in order to pass the muster of federal regulations. This reliance on the rare chance of benefit allows children to be put at great risk without concomitant benefit simply because there exists an off chance for an improbably good outcome. Yet, changing the regulations would not help us answer fundamental questions. These questions must be answered in the context of relationships themselves. Unfortunately, as we saw in *Chapter Three, Chapter Four,* and *Chapter Five*, phase 1 trial enrollment does not hold up under relational scrutiny. Phase 1 trials do not provide a substantial mechanism for parents, children, and physicians to meet their relational obligations to one another in the face of grave illness. The real problem is perhaps that we have so long relied on

similarities between research and clinical practice when they are actually two very different endeavors. In the case of early phase research, clinical innovation provides a way forward that does not require us to sacrifice children's health or quality of life for a future good. Physicians will undoubtedly learn from this paradigm, as they have done in many clinical contexts; but they will do so by continuing to treat today's patients rather than foregoing their responsibilities in the hopes of a better future. None of us is guaranteed the future; we are still obligated to today.

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