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Dying Children and Medical Research: Access to Clinical Trials as Benefit and Burden

Michelle Oberman\textsuperscript{1} & Joel Frader\textsuperscript{2}

I. INTRODUCTION

There is perhaps no greater tragedy in a parent's life than learning that one's child is terminally ill. Today, more than at any time in the past, when conventional treatment fails, dying children are given access to experimental treatment. To a surprising extent, society takes for granted the participation of dying children in medical experiments. In part, this is because we have come to view participation in clinical trials as a potential benefit. This view contrasts sharply with the dominant perception of the mid to late 20th century, which viewed medical research as a potential threat to vulnerable populations. Upon closer scrutiny, both of these perspectives carry with them some important truths. This Article seeks to build upon those truths by undertaking a critical analysis of contemporary ethical and legal policies governing the inclusion of terminally ill children in clinical research.

Well-documented abuses of human subjects in medical experimentation, including research with children, created concern in the latter decades of the 20th century. This led to the perception that children were vulnerable, given their inability to protect their own interests, and that the mere fact that parents gave informed consent was insufficient to safeguard their children from the potential harms of medical experimentation. Federal regulations put into place in 1981 sought to provide the necessary additional safeguards. Such rules might have led to a relatively small percentage of sick children enrolling in clinical trials in pediatric oncology. Yet today, a strikingly large majority of U.S. children with cancer are enrolled in Phase III clinical trials and receive therapy under experimental conditions. This is unlike the situation of adults with cancer, where approximately

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fifteen percent participate in clinical trials. The overwhelming majority of children with cancer become subjects in medical experiments.

These numbers might be unsurprising as pediatric cancer research involves children suffering from life-threatening diseases, which until the 1960s had virtually no effective therapy. In the mid-twentieth century, clinicians and families agreed that clinical studies offered the best chance to save the lives of the affected children. The partnership between pediatric cancer research and clinical studies proved remarkably effective. In less than half a century, clinical research in pediatric oncology produced great progress. The most common form of childhood leukemia went from being a nearly always fatal disease to one cured more than seventy-five percent of the time. Such success no doubt contributed to a willingness to permit children to become the subjects of medical experiments, and perhaps reflected a more general shift in American thinking about the nature of medical research. Beginning in the mid-1980s, in response to scientific progress achieved through clinical research in cancer and AIDS, Americans began to demand access to clinical trials.

These factors help to explain the high percentage of children with cancer who participate in clinical studies, and may also explain the limited ethical and legal scrutiny this issue has received. It may seem needlessly academic to analyze the pros and cons of enrolling pediatric cancer patients in clinical trials. Nonetheless, it is far from clear that the sickest of children—those whom conventional treatment cannot cure—personally benefit from enrollment in early-phase studies.

To the extent that we fail to explore the legal and ethical issues surrounding children’s participation in clinical studies, particularly in Phase I clinical trials, we run the risk of replicating the historical abuses of this exploitable population. Toward this end, this Article undertakes a critical analysis of the legal and ethical norms governing the enrollment of sick children in early-phase trials. The Article begins with a brief overview of the history of medical experimentation involving children, assessing both its great promise and its inherent limitations. Part II describes contemporary practices governing research with this population, particularly in regard to Phase I studies. Part III then explores the key legal and ethical problems with the manner in which Phase I pediatric trials are conducted. Finally, the Article concludes by exposing, critiquing and refining the justifications for and the ramifications of permitting and promoting children’s access to Phase I trials.

II. A BRIEF HISTORY OF MEDICAL RESEARCH INVOLVING CHILDREN

Since the dawn of modern public health medicine in the West, there has been a remarkable transformation of childhood morbidity and mortality. In the past two hundred years, infant and child mortality has plummeted. In just the last fifty years, research has led to cures for many, if not most, of the common childhood illnesses and many of the ravages of premature birth. Children with major chronic conditions, such as cystic fibrosis, diabetes and sickle cell disease, used to die before reaching the age of majority. Now many live well into adulthood. As a result, parents in Western industrial or post-industrial societies now expect their children to survive and thrive—even children with life-threatening disorders.

During this period, some “medical progress” has come with a high price: undignified and harmful research practices involving children and others unable to
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protect themselves. Beecher documented several of these cases in a landmark paper in 1966:1

- In an effort to learn about the functional anatomy of the urinary tract, doctors inserted catheters into the bladders of healthy newborns, injected radio-opaque dye and performed multiple X-ray studies.
- Physicians suspected liver injury might result from administration of an antibiotic. Investigators administered the drug to "inmates of a children's center," including "mental defectives or juvenile delinquents" without any "disease other than acne." The researchers stopped the study early because of "high incidences of significant hepatic dysfunction." Several subjects subsequently required liver biopsies.2

Beginning in the 1970s, governments and professionals acted to prevent research-related harms to those lacking adequate decision-making capacity.3 In the United States, decades-long practices of the Food and Drug Administration (FDA) tended to exclude children from research aimed at establishing the safety and efficacy of new medications. Regulations regarding human research subject protection included special sections restricting the inclusion of minors in clinical studies.

This regulatory process—and parallel concerns about prolonged liability that might result from claims about research-related harms to children—had a double-edged effect. The regulations required researchers to demonstrate that the benefits of the proposed research outweighed the possible burdens to child subjects. As such, the regulations called attention to the developmental vulnerability of children who were potential research subjects. This caution may have helped to prevent unnecessary, or simply foolish, harms to children from medical studies. On the other hand, the bureaucratic hurdles and liability fears have no doubt slowed, or in some cases, halted potentially valuable biomedical progress.

Concern over the latter possibility has led to federal policy changes in recent years. Beginning in 1998, for example, Phase III clinical trials conducted with the support of the National Institutes of Health (NIH) were required to include children or provide a justification for their exclusion.4 The FDA also requires companies to include children in their new drug approval process, using both incentives and penalties to insure compliance. In addition to rejecting studies that unjustifyifiably limit access to children, the FDA encouraged companies to conduct research regarding the pediatric safety of already marketed drugs by providing a six-month

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2 Id. at 1354-60.
4 However, an oddity in the definition of "childhood" used by the NIH permits an end-run around this objective. The NIH defines children as "individuals under the age of 21." NAT'L INST. OF HEALTH, NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (1998), at http://grants1.nih.gov/grants/guide/notice-files/not98-024.html. Therefore, by allowing eighteen to twenty-one-year-old adults to count as children, one can meet the NIH requirement of inclusion without performing physiologically meaningful studies to assess children's vulnerability to medication at various stages prior to full adulthood.
This policy shift in favor of including children in clinical studies occurred as part of a broader movement wherein consumer groups demanded access to clinical trials. By the mid-1980s, the absence of effective treatment, much less cures, for AIDS led advocates to demand access to clinical trials arguing, "A Drug Trial is Health Care Too." This campaign helped to transform the public perception of medical experimentation from a risky, exploitative venture into the best response to an incurable disease. Then in the 1990s, advocates for women's health endorsed this image of medical research by decrying the decades-long exclusion of women of reproductive age from clinical research and the resulting ignorance about the safety and efficacy of treatments when used by women.

Progress in the development of treatments for HIV and cancer, among other conditions, has transformed society's perception of the nature of medical research, making inclusion much more desirable than previously perceived. Nonetheless, the same justifications for access to clinical trials may not apply with equal force to those who have exhausted their options for established therapy, or Phase II and Phase III studies, and have become eligible for Phase I studies. This is particularly true for sick children.

There has long been considerable debate about the acceptability of children as subjects of biomedical and behavioral research. At least as far back as the publication of the Nuremberg Code on human experimentation, and the subsequent first Declaration of Helsinki on that same topic, renowned ethicists have argued that children must not be subjected to medical experimentation. The extended exchange in the 1970s between Paul Ramsey and Richard McCormick highlights the ethical issues. Children, at least prior to achieving some level of intellectual sophistication and emotional maturity, cannot make autonomous decisions about whether or not to enroll in studies. Ramsey, consistent with the Nuremberg Code, felt that the inability to give consent precluded including children in medical research unless participation held out a prospect of providing individual benefit. McCormick, in contrast, maintained that such wholesale exclusion of children resulted in disadvantaging the entire class of minors. Further, he argued, assuming tolerable, or in his words "no realistic" risks, children ought to participate in research precisely because such participation would benefit others.

The moral issues have changed little from the 1960s and '70s when these debates occurred. They emerge with particular clarity when considering the

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participation of children in Phase I clinical trials, which are intended to establish, "toxicity, metabolism, absorption, elimination, and other pharmacological action...." The design of a Phase I study generally involves placing participants on escalating doses of a study drug and observing them to determine the maximum dose at which the drug can safely be tolerated. To the extent that there is any therapeutic benefit to participation in such a study, it is incidental, or indeed coincidental, to its central purpose.

With respect to Phase I clinical trials in pediatrics, we need to establish the extent to which it is ever appropriate for children to participate. What are the benefits of participation and to whom? What are the risks associated with enrollment in such studies? How can one make reasonable determinations about the balance between benefits and risks for a given study or a given prospective enrollee? The following section begins with a descriptive overview of contemporary pediatric research practices in the Phase I context. Thereafter, it undertakes to answer these questions via a critical analysis of the legal and ethical issues raised by current policies governing the inclusion of children in clinical research.

III. DYING CHILDREN AND MEDICAL EXPERIMENTATION: AN OVERVIEW OF PHASE I RESEARCH WITH CHILDREN

Scientific progress in treating and curing pediatric ailments, whether in oncology, HIV treatment, cardiology or any area of pediatric medicine, depends upon conducting clinical trials as rigorous and thorough as those in adult medicine. In order to safely introduce new treatment regimens for children, pediatricians must conduct Phase I, II and III trials. Children differ physiologically from adults, so without doing parallel studies, one would not know proper dosing for children, the range of side effects new medications produce in children or whether the drugs work as intended in children. If one relies only on the results of trials conducted in adults, physicians risk substantial harm to children, either in the form of unrevealed toxicity or false hopes that drugs will help children when, in fact, they may not help despite benefits for adults. The antibiotic chloramphenicol, for example, proved life-saving in many cases of bacterial infection in adults and older children when first introduced, but when given to infants, the drug can rapidly produce fatal shock.10

Treatments for conditions that occur exclusively or much more commonly among children than adults do not undergo clinical trials in adults. In such circumstances, the only way to introduce new medications for use with children involves trials in pediatrics. In each of these contexts, early-phase trials in which investigators seek to discern evidence regarding such things as toxicity and maximum tolerated dose, enrollment may not provide a meaningful prospect of benefit to individual subjects. Conducting these studies is nonetheless necessary to confer benefits on future patients.

As compelling as they may be, these societal reasons favoring the performance of early phase clinical trials on pediatric subjects cannot be invoked as the sole justification for subjecting children to medical experimentation. American society

10 Charles F. Weiss et al., Chloramphenicol in the Newborn Infant: A Physiologic Explanation of Its Toxicity When Given in Excessive Doses, 262 NEW ENG. J. MED. 787, 787 (1960).
values individualism and autonomy over communitarian or altruistic values. Thus, it is not enough to say that because these studies will benefit other sick children in the future, it is permissible to place these sick children at any level of risk. In order to justify their inclusion, we must balance the risks inherent in participation in Phase I research to individual children against whatever benefits might accrue.

Identifying subjects for Phase I research often has been a problematic and controversial process. This is inherent in the design and function of Phase I research, which is not focused on the goal of treating, let alone curing the participant. Rather, the focus is on establishing the manner in which a given substance or treatment affects the human body. Unlike later phase trials, which focus on safety, efficacy and refining dose, Phase I trials hold out little hope of benefiting the participant, save by pure coincidence. In the context of clinical research with adults, sponsors and investigators often have used marginally ethical means of enrolling participants in such trials.

The problem of identifying children for Phase I research is both more and less challenging than that of identifying adults. Federal regulations greatly limit the extent to which children may become subjects in non-therapeutic research (i.e., any experiment that holds out no possibility of benefit to the individual). Consequently, in virtually all cases, pediatric Phase I studies are performed on children who are sick and might conceivably benefit from the study. A Phase I pediatric study, for example, may involve a substance that, because it works for some adults, is thought to have promise for children as well. Phase I studies in pediatrics most commonly involve children who have not responded to conventional treatment. The practical reality is that children in Phase I studies tend to be very, very ill.

Assessing the risks and benefits of participation in Phase I clinical trials is complicated. Theoretically, it should be easy to measure benefit in studying the outcomes of Phase I clinical trials. A benefit would be construed as the achievement of a cure, remission or amelioration of symptoms. In one of the only studies on this topic, researchers reviewed the overall response rates of 577 children with pediatric cancer who were enrolled in Phase I studies in the 1970s and ‘80s. The researchers noted a 5.9% response rate, meaning that thirty-four of the children achieved a complete or a partial remission of their disease. The majority of these remissions were partial, however, and the median duration of the eleven “full remissions” was only sixty days. Thus, as Professor Terrence Ackerman notes in his 1995 critical review of Phase I pediatric oncology studies, over 98% of participants got no benefit at all. Fewer than 2% of participants achieved what is termed a “complete remission,” which lasted only for an average of two months, after which the disease returned.

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12 To be sure, there may be psychic benefits gained by one who elects to undergo medical experimentation for altruistic reasons. These benefits are hard to measure, even when evaluating adult volunteers. The extent of their relevance in pediatric studies, particularly in those involving the youngest participants, is questionable. See infra Part IV for a discussion of evidence indicating that the desire for personal benefit, rather than altruism, is the central motivation behind adult participation in clinical studies.
14 Terrence F. Ackerman, The Ethics of Phase I Pediatric Oncology Trials, 17 IRB 1, 2 (1995).
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Recent data echo these findings. In a review of Phase I cancer studies at a major research center, the authors noted an overall "response rate" of 3%. One percent of the subjects died as a result of toxic effects of the experimental agents. A 1998 review article stated that, "5-7.5% of children who enter Phase I trials achieve either a partial or complete response," meaning regression or disappearance of measurable tumor. The paper also notes that many children enrolled on Phase I studies have experienced "heavy pretreatment" as part of earlier efforts to bring about a cure. As a result, they may have less tolerance for toxic agents than would healthier children. This makes it harder for researchers to ensure the accuracy of their findings. It also may make the Phase I study riskier, and less likely to yield benefit, to the sick participant. Finally, another review of Phase I pediatric cancer trials conducted between 1978 and 1996 reported an "overall objective response rate" of 7.9%. The range of tumor response spanned less than 3% of subjects in a trial to as many as 17.7%, depending on the type of cancer and agent used. Only 0.7% of the enrolled subjects were thought to have died as a direct result of drug toxicity.

There may be a trend towards a higher rate of tumor response in more recent trials. Nonetheless, it is important to bear in mind the limited nature of what is meant by "response rate." Specifically, a finding of a "response" to a study drug does not imply that the participants' conditions went into full remission, let alone that they were cured. Indeed, a response may mean nothing more than that the size of their cancer was reduced to some degree. This reveals little about the extent to which the treatment lengthened lives, improved symptoms or contributed to overall patient/subject well-being. Furthermore, the assessment of the individual benefits and risks of participation has suffered because of the questions that go unasked about the quality of life for children enrolled in these Phase I studies. Did the clinical trial enhance or impede the individual's dying process? Did enrollment in a clinical trial limit eligibility for or receipt of palliative and hospice care?

Outside of the Phase I context, some evidence suggests that enrollment in clinical trials, in and of itself, produces better outcomes. Phase III studies evaluate medical interventions that have shown promise and established safety. Phase III studies generally use a relatively large number of participants and aim to determine efficacy under optimal clinical circumstances. Evaluations of a series of Phase III pediatric oncology and neonatal intensive care studies suggest that children enrolled in therapeutic trials have better outcomes than those receiving similar treatment outside of the research context. A recent report from Switzerland echoes this finding.

15 The paper does not note the ages of the participants studies analyzed, but instead infers that they are adults or that the majority of participants are near adulthood. T.L. Smith et al., Design and Results of Phase I Cancer Clinical Trials: Three-year Experience at M.D. Anderson Cancer Center, 14 J. Clinical Oncology 287, 293 (1996).
16 Id.
17 M. Smith et al., Conduct of Phase I Trials in Children with Cancer, 16 J. Clinical Oncology 966, 967 (1998).
19 Ackerman, supra note 14, at 2.
21 H.P. Wagner et al., Childhood NHL in Switzerland: Incidence and Survival of 120 Study and 42 Non-Study Patients, 24 Med. & Pediatric Oncology 281 (1995). For articles lending additional

The fact that study participants have better outcomes than those receiving treatment in the absence of a study is not entirely new or surprising. It seems that, at least with regard to Phase III controlled studies, there may be clinical benefits to being a research subject. Even if there is a beneficial effect associated with participating in Phase III clinical studies, there is little reason to assume that the same benefits would extend to participants in Phase I trials. Indeed, given the divergent aims of Phase I trials, such an assumption may be completely unfounded. Nonetheless, evidence of a positive value associated with Phase III study participation, coupled with the admirable determination of academic pediatricians to improve the outlook for their patients with life-threatening diseases, likely have contributed to the success in enrolling terminally ill children in Phase I clinical trials, in spite of the overwhelming odds against providing them with any meaningful relief.

IV. LEGAL AND ETHICAL COMPLEXITIES RAISED BY PHASE I TRIALS IN CHILDREN

Many of the problems Phase I research raises in children mirror those inherent in Phase I trials with adults: the misconception that such research represents “treatment,” and the potential for researchers to lose sight of their patient’s best interests as they simultaneously pursue roles as treating physicians and clinical investigators. When considering Phase I research in children, the unique nature of the relationships among parents, ailing children and physician-researchers complicates these problems considerably. In order to explore the problematic features inherent in Phase I research in children, this section begins with a discussion of the “therapeutic misconception.” The section then describes the challenges Phase I studies pose to the fiduciary nature of the doctor-patient relationship. Finally, the section closes with an analysis of the legal and ethical problems inherent in parental or proxy consent.

A. THERAPEUTIC MISCONCEPTION

Phase I studies are explicitly non-therapeutic in nature. Intended to reveal the pharmacological action of the study agent, the Phase I trial seeks to establish a baseline regarding toxicity before moving into the Phase II studies of safety and biological effects of the intervention. Many have noted the tendency of individuals involved in these trials to mistakenly perceive them as “therapeutic” or “potentially therapeutic.” This phenomenon, known as the “therapeutic misconception,” seems to be an understandable response of patients and family members when conventional therapies have failed to produce a cure. Physicians approach family members with the news that no established treatments offer the potential for meaningful benefits, and the family then hears that a research trial exists in which they might participate. Patients, parents and older children may naturally view such research as their best support to these findings, see S.B. Murphy, The National Impact of Clinical Cooperative Group Trials for Pediatric Cancer, 24 Med. & Pediatric Oncology 279 (1995) and S. Schmidt et al., Do Sick Newborn Infants Benefit from Participation in a Randomized Clinical Trial?, 134 J. Pediatrics 151 (1999).

chance at survival. One survey of clinical researchers found that 94% agreed that adult patients enroll in Phase I studies "mostly for the possible medical benefit."23

These studies help give lie to the notion that patients volunteer for Phase I trials out of an altruistic desire to help others who may contract the same illness in the future, even when study personnel explicitly tell prospective study participants that the aim of the trial involves accumulation of knowledge for future patients. Patients and parents most likely volunteer because they nevertheless believe that they, personally, may benefit.

The confusion over the extent to which Phase I studies constitute "treatment" rather than non-therapeutic experimentation results from more than the sick patient's desperation to find a cure. The therapeutic misconception is fostered in part by those who purport to set standards for governing human research. The 1964 Declaration of Helsinki, for instance, sets guidelines for doctors in clinical research by classifying all research on humans into two categories: therapeutic and non-therapeutic.24 The Declaration terms some research "therapeutic" and blurs the line between research, the goal of which is the advancement of science, and treatment, the goal of which is to assist, if not to cure, an ailing patient. The National Cancer Institute goes further, calling Phase I studies (which would be "non-therapeutic" under the Helsinki Declaration) "potentially therapeutic."25

Perhaps the largest source of confusion regarding Phase I trials as "treatment" comes out of the process by which patients consent to participate in these trials. Professor Nancy King has pioneered several studies documenting the decidedly strategic use of language in consent forms for clinical trials. Working with co-author Gail E. Henderson, King has conducted research into the presentation of information in the relatively new field of gene transfer research and has found that consent forms frequently use language that connotes treatment rather than research.26 They reviewed consent forms from all gene transfer studies initiated between 1990 and 2000, and found that even though over half of the trials were Phase I, only 1% of consent forms stated unambiguously, "You will not benefit [from participation]."27 The tendency of consent forms to obscure the purposes of the proposed research and to exaggerate the potential benefits to participants make it no wonder that patients for whom conventional treatment has failed tend to mistake Phase I toxicity trials of new agents for "potential cures."

Consent forms aside, patients and families likely make trial participation decisions based, at least in part, on interactions they have with their treating physicians. Daugherty, an oncologist and ethics researcher, has documented that many oncologists share the therapeutic misconception. In spite of numerous studies showing that fewer than 10% of patients can expect even the most modest of

27 Consent Forms, supra note 26.
benefits from a Phase I trial, 18% of surveyed oncologists expected that subjects enrolled in Phase I trials would experience an “overall benefit,” while 15% felt subjects would have a tumor response to the Phase I agent(s). One has to wonder how such beliefs might, subconsciously or otherwise, affect communications with patients and influence trial participation.28

Pediatricians share these therapeutic misconceptions, and studies show that pediatric oncologists view enrollment of children as offering a benefit to individual subjects, despite trial designs dedicated to revealing “dose-limiting toxicity.” In a peer-reviewed article on clinical trials in children with cancer, Smith and colleagues assert “children are given drugs on Phase I studies with therapeutic intent.”29 An NIH-based group discussing pediatric oncologists’ views on end-of-life noted that in response to a vignette describing a child virtually certain to die of recurrent cancer, “20.1% of pediatric oncologists recommended active therapy” which included 12.3% recommending a Phase I trial.30 In contrast, an Italian research group writing about studies in HIV-infected women and children stated, “Phase I trails are nonclinical biomedical research that must be carried out on low-risk subjects.”31

The problem with therapeutic misconception is not that patients and loved ones experience feelings of hopefulness when offered the chance to participate in Phase I research. Certainly, there is nothing wrong with the fact that some patients may find psychological or spiritual benefits in doing “everything possible” to fight off their disease. The problem lies in the extent to which study personnel respond to the tendency of patients to mistake Phase I trials for medical treatment. Recall that most patients who consent to participate in Phase I research do so not for the “psychic” benefit, but because they mistakenly believe they will experience an actual benefit.32 The problem of therapeutic misconception therefore devolves into an issue of fiduciary duty: how far must a doctor or researcher go to ascertain the reasons behind a patient’s or surrogate’s willingness to participate in a Phase I trial?

B. FIDUCIARY DUTY AND THE DUELING ROLES OF DOCTOR AND RESEARCHER

For several decades, federal and state courts alike have acknowledged the fiduciary nature of the physician-patient relationship.33 In a fiduciary relationship, one party depends upon the other, trusting the other to act in his or her best interests. These relationships exist when the dependent or more vulnerable party delegates power to the fiduciary so that the fiduciary may act on her behalf. Professor Marc A. Rodwin describes the manner in which doctor-patient relationships resemble “classic fiduciary relationships”:

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31 M. de Martino et al., Human Immunodeficiency Virus Type I Infection, Clinical Trials, and Ethics in Pediatrics, 421 ACTA PAEDIATRICA 78, 82 (1997 Supp.).
32 See Daugherty, supra note 28.
33 Marc A. Rodwin, Strains in the Fiduciary Metaphor: Divided Physician Loyalties and Obligations in a Changing Health Care System, 21 AM. J.L. & MED. 241, 241-42 (1995) (noting that “[t]he idea that physicians are or should be fiduciaries for their patients . . . is a dominant metaphor in medical ethics and law today”).
Physicians have specialized knowledge and expertise. They also control the use of medical resources needed by patients: only they can admit patients to hospitals, order diagnostic tests, and prescribe drugs. Patients are often ill or anxious about their health, which increases their dependence. The patient-physician relationship presupposes patients entrusting physicians to act on their behalf and physicians remaining loyal to their patients.\(^3\)\(^4\)

Central to the notion of fiduciary duty is the recognition of the potential for the fiduciary to experience divided or conflicting loyalties. Fiduciary law seeks to resolve these conflicts by mandating priorities for the fiduciary in the event of a conflict. The current structure of the U.S. healthcare system generates a host of fiduciary challenges for physicians, virtually all of which relate to forces that compete with doctors’ obligations to their patients. In the managed care setting, conflicts arise when physicians must act as gatekeepers, minimizing patients’ access to expensive tests or contacts with medical sub-specialists. More dramatic conflicts exist in “gag clause” contracts, which prohibit physicians from advising patients about alternative courses of action not offered under the patient’s insurance package. Additional fiduciary challenges arise in the area of confidentiality, when a physician may have a moral, or even a legal, duty to inform a third party about her patient’s private medical condition. Finally, one finds fiduciary conflicts in obstetrical medicine, when doctors threaten to undermine their pregnant patients’ autonomy rights by imposing a particular course of action upon them in the name of protecting their fetuses.\(^3\)\(^5\)

Fiduciary conflicts in the clinical research setting grow out of doctors’ divided loyalties when they attempt to function both as physician and as researcher. This conflict can exist at several levels. The treating physician also may have a role as developer of an institutionally approved study directly relevant to the patient’s condition. As the originator of the research, the physician-investigator has a scientific interest in seeing her idea tested. She also may have understandable enthusiasm for and a not-so-objective bias in favor of the experimental intervention. Such principal investigators might have difficulty maintaining neutrality when communicating the availability of the trial to patients and family members. More commonly in academic centers conducting controlled trials, treating physicians have roles as “co-investigators,” in which they expect to “offer” open research protocols to patients meeting study criteria. In such settings, institutional pressures favor patient enrollment. Centers have to enter minimum numbers of subjects into trials in order to maintain their status as members of the cooperative group. Payments to support the clinical research enterprise at a center often depend on the absolute number or percentage of eligible patients enrolled as subjects. An individual’s academic advancement (e.g., promotion in the professorial ranks) may depend on how quickly studies fill, and on how soon and how often the physician-researcher

\(^3\) Id. at 245-46.

publishes papers discussing research results. Many environmental pressures favor enrolling patients in trials, and being the treating physician and researcher or researcher's colleague may confuse the individual's responsibilities.

This blurring of roles can pose problems because unlike the "pure" physician, whose primarily obligation involves safeguarding her patient's health, the researcher has additional goals stemming from an interest in promoting the accumulation of scientific knowledge, supporting one's program or institution, career advancement, or in some cases, direct financial gain. Recently, these factors came to bear in the context of one particularly notorious pediatric Phase I trial. The trial involved gene transfer experiments regarding ornithine transcarbamylase (OTC) deficiency at the University of Pennsylvania. This Phase I study received critical national attention after one subject, Jesse Gelsinger, died. Subsequent investigations revealed that there were apparent, if not actual, financial conflicts of interest for the investigators because both the principal investigator and the University had substantial equity interests in the company developing the viral vector used to deliver a normal gene into subjects' livers. According to the FDA's final assessment of the case, Gelsinger underwent the intervention despite considerable information that the experiment should not go forward.36

Patients may find it difficult to recognize when their doctor has switched hats and is acting primarily as an investigator rather than as a treating physician focused exclusively on patient benefit. Patients with chronic, terminal illnesses often develop close, trusting relationships with their physicians over the course of months, or even years. These individuals and families, having exhausted conventional treatment options, may have difficulty knowing how to respond when the doctor-cum-Phase I-researcher approaches them about an open study concerning the condition.37

Researchers generally are not motivated by selfish goals. They believe clinical investigations constitute the only valid mechanism for advancing toward a cure for the patient's illness, even if the study at hand has little likelihood of helping the individual patient. Nonetheless, when the terminally ill patient's doctor offers participation in a Phase I trial, patients and family members tend to hear a recommendation to enroll. As a result, Professor Annas argues that physicians should not be permitted to play both roles:

> It is unlikely that it will ever be possible . . . for patients not to indulge in self-deception by imagining that research is really treatment and that they are patients, not research subjects. We cannot separate the subject into two persons. But we can assure that the subject-patient always has


37 As Professor Annas notes, "When physician and researcher are merged into one person, it is unlikely that patients can ever draw the distinction between these two conflicting roles because most patients simply do not believe that their physician would knowingly harm them or would knowingly use them as a means for their own end." Annas, supra note 9, at 311-12.
a physician whose only obligation is to look out for the best interests of the patient. Thus, we can (and should) prohibit physicians from performing more than minimal risk research on their patients, and as a corollary, only permit physician-researchers to recruit the patients of other physicians for their research protocols. In this way, at least the “doubling” of physician and researcher can be physically (and perhaps psychologically) eliminated.38

The law could, and perhaps should, go farther in regulating these conflicts of interest. The law of fiduciary obligations should address the potential for abuse of power inherent in the physician/researcher confusion by invoking legal mechanisms to promote fiduciary accountability. Others have noted the limitations on plaintiffs who seek to sue their physicians for breach of fiduciary duty.39 The restrictions derive largely from the law’s conflation of medical negligence and fiduciary duty as legal causes of action. This leads judges to reject cases in which the plaintiff has not been harmed as a result of the doctor’s malpractice. Recent cases, however, have witnessed an expansion in the law’s understanding of the physician’s role as a fiduciary.40 As a result, mechanisms to reign in the abuse of fiduciary power in non-medical settings should become available in the clinical research context. These methods include reducing the fiduciary’s discretion by regulating their range of permissible activities, supervising the fiduciary and penalizing those fiduciaries that breach their client’s trust.41 All three of these tactics could be applied to those who overstep fiduciary bounds in clinical research.

What we know about the clinical benefits of Phase I trials, and about patients’ tendencies to misconstrue the nature of these trials, indicates that obtaining consent to Phase I trials is fraught with the potential for breaching fiduciary duty. The physician may breach her fiduciary duty whenever she secures her patient’s agreement to enter a Phase I trial without having assured that the patient understands the low likelihood of therapeutic benefit and the physician’s role as researcher.

In the context of Phase I pediatric clinical trials, the problem of physicians’ divided loyalties is far more than a theoretical threat to patient autonomy. Instead, it operates in the context of parental grief and desperation, often fueled by the problem of therapeutic misconception, to create a powerful impetus toward enrolling dying children into non-therapeutic research studies.

38 Id. at 322.
39 Oberman, supra note 35, at 458-59 (citing Rodwin, supra note 33, at 247-48).
40 For example, the California Supreme Court held that a plaintiff’s complaint stated a cause of action for breach of fiduciary duty where a surgeon failed to disclose his research and financial interests when obtaining the patient’s informed consent for the procedures. Moore v. Regents of Univ. of Cal., 739 P.2d 479, 485 (Cal. 1990). Applying Minnesota law, the Eighth Circuit went further and commented that even when not recommending courses of treatment, physicians have fiduciary duties to disclose conflicting loyalties. Shea v. Esensten, 208 F.3d 712, 717 (8th Cir. 2000). The court recognized a financial interest in an HMO contract designed to minimize referrals as a conflicting loyalty. See id. at 717. But see Neade v. Portes, 739 N.E.2d 496, 498 (Ill. 2000) (refusing to impose a duty on physicians to disclose HMO financial incentives for reducing referrals for outside testing and specialists).
41 Rodwin, supra note 33, at 247.
C. PARENTS AND PROXY CONSENT: THE CONFLUENCE OF THERAPEUTIC MISCONCEPTION, BREACH OF FIDUCIARY DUTY AND PARENTAL GRIEF

In pediatric clinical trials, one easily can discern how the problems of therapeutic misconception, coupled with the doctor's divided loyalties, intensify. The inherently challenging process of identifying and honoring patients' autonomous choices regarding participation in research is greatly complicated when the patient is a minor. For theoretical and practical reasons, the fact that the study participant is a minor complicates valid authorization of enrollment in fairly obvious ways. The law generally does not permit minors to consent to their own healthcare, much less to authorize research enrollment; therefore, the minor's guardian, typically the parent(s), must decide whether to permit the child to enter a trial.

The notion of informed consent grows out of the core ethical value of autonomy. The mere presence of a third party decision-maker poses a threat to the child's autonomy rights. When faced with the necessity of medical decision-making for incompetent adults, the medical and legal systems attempt to preserve respect for patient autonomy by requiring the surrogate to make a decision using "substituted judgment." This involves instructing the surrogate decision-maker to infer what the incompetent person would decide were he or she able to do so.

This cautionary guidance does not readily apply to parental decision-making for children. Under ordinary circumstances, society expects parents to reflect upon the medical information they have been given and decide about the child's treatment based on a "best interests" standard. In the research context, the Belmont Report, and much of the bioethics literature, refers to "parental permission," omitting altogether the more legally charged term "consent." Regardless of the terminology, this legal structure permits doctors and investigators to treat or study children without having to first ascertain whether the child either desires the intervention or considers it in his or her best interest. Federal research regulations acknowledge the problem and have attempted to address it by, at least in some circumstances, requiring the minor's "assent" in addition to parental consent to research. As Professor Jennifer Rosato has persuasively argued, however, the concept of "assent" lacks legal force, does nothing to protect the interests of those

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42 In addition, the state plays a role in medical decision-making for minors, limiting parental authority over children through the doctrine of parens patriae. This doctrine provides that the state limits parental authority to the power to act in a child's best interest. To the extent that the state perceives a parent's action as inconsistent with a child's best interest, the state will intervene to order proper medical care. Although there is a line of cases where the state has ordered medical treatment that was refused by a parent, none of these cases involve experimental care. This may be because courts acknowledge that while states "may not permit a parent to deny a child all treatment for a condition which threatens his life," it is not for them to determine the most "effective" treatment "when the parents have chosen between reasonable alternatives." Crouse Irving Mem. Hosp. v. Paddock, 485 N.Y.S.2d 443, 444-45 (1985) (upholding order for blood transfusions, despite religious objections, for both mother and baby during a Cesarean section delivery, citing In re Matter of Hofbauer, 419 N.Y.S.2d 936 (1979)).


deemed too young to assent and does little to ensure a right to refuse for those teens who do not wish to become research subjects.\(^4\)

The absence of a substituted judgment model for parental decision-making suggests that we view the parent-child relationship as unique and regard children and their parents, in some sense, as a single unit. The law solidly supports this notion, assuming that parents will act in their child's best interests.\(^4\) Everything we know about therapeutic misconception, fiduciary conflicts and the grief of parents whose child is dying should lead us to question the extent to which, in the context of Phase I trials, we can reasonably ask parents of dying children to act purely in the child's best interests.

Others have described the range of emotions that accompany a parent's response to the end stages of a child's terminal illness. A parent may retain unrealistic hope for improvement in the face of worsening illness.\(^4\) A parent may consent to research in an effort to obtain a sense of control over the dying process. Having worked with a particular physician or team of physicians over the course of the child's illness, parents may accept Phase I research because they fear losing both their own and their child's relationships with the healthcare providers who have worked so hard to save their child's life.\(^4\)

We should not fault parents motivated by any of these reasons when authorizing a child's participation in Phase I research. To a large extent, they seem to represent the normal responses of loving parents to the tragic circumstances of a child's terminal illness. Still, these reasons differ markedly from those ideally motivating the enrolling of a terminally ill patient in a Phase I clinical research project.

Present practices governing Phase I pediatric trials ignore the ethical dilemma inherent in the assumption that parents objectively can assess the "best interests" of their dying child. Recall that parents enrolling their children in Phase I trials are vulnerable to mistaken beliefs that such research will be not only therapeutic but curative, and that their child's doctor, in recommending participation, is acting purely on behalf of the child's interests. Researchers generally take parental "consent" at face value. They assume that parents make fully informed, carefully considered decisions when permitting their child to participate in such research, and see it as unnecessary, and perhaps intrusive and inappropriate, to take substantive measures to ensure the "quality" of parental decision-making.

The fact remains that the odds do not favor a child's receiving any therapeutic benefit from participating in a Phase I study. There is a substantial risk that participation may cause discomfort, interfere with palliative care or occasionally hasten death. As such, the fact that those responsible do little to ascertain parental understanding and motivation when enrolling their child in a Phase I trial may be viewed as a reflection of a systemic bias in favor of enrolling the child in the


\(^4\) This presumption is not without its shortcomings. See generally JOSEPH GOLDSTEIN ET AL., BEYOND THE BEST INTERESTS OF THE CHILD (2d ed. 1979) (focusing on the area of child placement and the impact of parental decision-making on the child's psychological development). For a fascinating critique of the legal system's failure to recognize children's rights, see Jane Rutherford, One Child, One Vote: Proxies for Parents, 82 MINN. L. REV. 1463, 1525 (1998) (suggesting a model in which parents can represent their children's political views).

\(^4\) Ackerman, supra note 14, at 4.

\(^4\) Ackerman, supra note 14, at 4 (citing S.C. Harth et al., The Psychological Profile of Parents Who Volunteer Their Children for Clinical Research: A Controlled Study, 18 J. MED. ETHICS 86 (1992)).
research, as opposed to considering each child’s actual, complex interests at the end of life. The current system encourages parents to consent in accord with researchers’ views that progress depends on conducting early phase research. Clinical investigators live with a terrible and irreducible tension. They have a fiduciary duty to pursue the patient’s best interest and a communitarian duty to obtain the knowledge necessary to advance the care of future patients.

V. CONCLUDING THOUGHTS TOWARD PROMOTING SAFE AND ETHICAL PRACTICES IN PEDIATRIC CLINICAL TRIALS

This tension challenges not only physicians, but also all those concerned with protecting the best interests of children. Some commentators attempt to resolve the inherent tension by suggesting that participating in research teaches children to value contributions to their community and therefore it constitutes part of their moral education. Society wants children to become altruistic, but it requires little reflection to see that such a justification does not readily apply to early phase clinical research with children in terminal stages of their diseases. Others offer family-centered justifications for children to become Phase I subjects. These suggest that parents have the legal authority to make all decisions regarding their child’s healthcare, and were society to limit the access of children to clinical trials, this would strip both children and parents of this right. This approach assumes that any decision-making regarding enrollment in pediatric clinical research reflects a careful assessment of the child’s best interest. A close scrutiny of the nature and purpose of Phase I studies reveals such an assumption to be dubious, at best. It succeeds only to the extent that (1) burdens to the child do not exceed some difficult-to-define threshold, and (2) Phase I trials actually represent therapy, not some illusion of treatment. Recognizing how untenable these individual-based claims are, some might move beyond the individual’s best interest and articulate a family-centered justification that suggests that parents and other loved ones who survive the child have an interest in knowing that they pursued any and all available means to prolong life.

Both of these justifications attempt to locate benefit in the individual or family unit in order to avoid the problem of endorsing consequentialist reasons for enrolling children in Phase I studies. The legal and ethical obligation to safeguard the individual’s best interest is undermined if the principle justification for permitting children to enroll in Phase I studies is that medical progress is a benefit to the community. In view of legal and ethical obligations, justification for conducting Phase I pediatric trials for the benefit of future children (i.e., accepting the consequentialist reasons to enroll children in Phase I studies) exists only if the individual, or at least the familial, reasons favoring inclusion are equally compelling. Such trials are ethically permissible only to the extent that there remains an unwavering commitment to protecting any given child’s well-being during the dying process.

49 For a discussion of this debate, see Terrence F. Ackerman, Fooling Ourselves with Child Autonomy and Assent in Nontherapeutic Clinical Research, 27 CLINICAL RESEARCH 345, 345-48 (1979).

Research on the consent process may provide avenues for substantially improving parental understanding of the particular benefits, risks and alternatives to participation in a given clinical trial. Truly informed consent to participate in a Phase I research study must ensure that the participant or her guardian(s) manifest a thorough understanding of (1) the risks and benefits inherent in the research, (2) the fact that the trial does not properly constitute treatment and (3) the fact that participation is unlikely to extend survival. Parents must be informed about the extent to which participation in any given study may cause additional pain or emotional distress as a result of the interventions, including discomfort associated with not-otherwise-indicated diagnostic procedures. Finally, parents must be told of the possibility that the experiment may hasten their child’s death or have a negative effect on possible palliative/hospice care alternatives. Failure to ensure that parents fully understand these matters constitutes a breach of the physician’s fiduciary duty to the patient.

Strategies for ensuring this commitment to the child’s welfare might include video or computer-assisted educational materials. Another strategy might be mandatory waiting periods between the first approach about a study and final authorization. This might provide better opportunities to review consent documents and consult with trusted advisors. Additionally, there could be required use of human subject “consent advocates.”

Ultimately, it may be impossible to articulate a rational justification consistent with our ethical commitment to safeguarding the individual’s best interest in favor of Phase I research in children. In a sense, these trials represent a societal death ritual: this is the way in which our society presently permits parents to grieve the horror of grave illness and premature death in children. This is also the way our society engages in a collective struggle against the scourge of terminal childhood illnesses. Law and tradition in medical ethics insist on the paramount value of the individual child’s best interests in medical decisions regarding minors. It may be that we have to accept that participation in Phase I studies embodies our hopes—no matter how unrealistic—and our fears of the premature death of our children and simply outweighs our rationality. While that may be so, if we are to escape the reviled tendency of past generations to willingly exploit vulnerable populations in the name of “scientific progress,” these studies must go forward with a keen awareness of the powerful duty owed to children by healthcare professionals, parents and the state: “to comfort always.”