

Nova Law Review

Volume 42, Issue 2

2018

Article 4

The Race Against The Clock: A New Bill Providing Hope For Children Fighting The Ultimate Battle

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Abstract

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THE RACE AGAINST THE CLOCK: A NEW BILL PROVIDING HOPE FOR CHILDREN FIGHTING THE ULTIMATE BATTLE

NICHOLAS M. FIORELLO*

I.	INTRODUCTION.....	256
II.	CHILDREN IN MEDICAL RESEARCH: UNREGULATED RESEARCH TO PARANOIA TO MODERN DAY	260
	A. <i>The Negative Connotation Attached to Pediatric Studies: The Result of Historical Abuses</i>	261
	B. <i>Responses to Medical Abuse of Children</i>	262
	C. <i>Pediatric Involvement in Clinical Studies for Childhood Cancer</i>	266
III.	THE CARROT AND STICK APPROACH: THE FDA’S TANDEM SYSTEM DESIGNED TO CHANGE THE LANDSCAPE OF PEDIATRIC MEDICINE.....	269
	A. <i>The Incentive-Based “Carrot”: The Best Pharmaceuticals for Children Act</i>	270
	B. <i>The Pediatric Research Equity Act: The “Stick” to the BPCA’s “Carrot”</i>	272
	C. <i>Results Following BPCA 2002 and PREA 2003: The Reenactment of the Carrot and Stick Approach</i>	273
	1. Revival: The Reenactment of the “Carrot and Stick”	276
	a. <i>The BPCA of 2007</i>	277
	b. <i>The PREA of 2007</i>	277
IV.	RACE: THE RESEARCH TO ACCELERATE CURES AND EQUITY FOR CHILDREN ACT.....	278
	A. <i>The Issues RACE Aims to Resolve</i>	279
	B. <i>RACE to the Finish: The Impact of this Proposed Legislation</i>	281
V.	CONCLUSION	282

I. INTRODUCTION

Roughly forty-three children are diagnosed with cancer daily.¹ Approximately 1190 children are expected to die from pediatric cancer this year in the United States alone—as the disease is the leading cause of death in children and adolescents, ages 1–14, in the country.² More than 40,000 children suffer through cancer treatment every year and, to add insult to injury, roughly 15,700 more children will be diagnosed with pediatric cancer this year alone.³ A child of any age, ethnicity, gender, or socio-economic group can fall victim to a pediatric cancer diagnosis.⁴

Despite leading to the most disease-related deaths among children, along with encouraging advances in the entire cancer research field, children usually are not the recipients of the new and promising drugs and treatments resulting from those advancements.⁵ This stems from the rarity of pediatric cancers, which represents less than one percent of newly diagnosed cancers each year in the United States.⁶ In turn, with comparatively fewer patients, the pediatric cancer market does not offer enough return for pharmaceutical companies to invest in developing and testing drugs specifically designed to target pediatric cancers.⁷ Peter C. Adamson, M.D., who is the Chair of the

* First and foremost, Nicholas M. Fiorello dedicates this Comment in loving memory of his brother, Adam Fiorello, who unfortunately lost his battle to Alveolar Rhabdomyosarcoma, a rare pediatric cancer. Nicholas earned his Bachelor's in Environmental Science at Florida State University. He is currently a Juris Doctor Candidate for May 2019 at Nova Southeastern University, Shepard Broad College of Law. Nicholas would like to thank his parents, Heidi and Michael Fiorello, for their unconditional love, support, and instilling the importance of hard work and the necessity of passion at an early age. He would also like to thank his friends and professors for constantly pushing him beyond his limits and positively influencing his legal education. Lastly, Nicholas would like to graciously thank his fellow colleagues of Nova Law Review, Volume 42, for the hard work, dedication, and time spent refining and perfecting this Comment.

1. Geoff Duncan, *Childhood Cancer Statistics*, CURESEARCH, <http://curesearch.org/Childhood-Cancer-Statistics> (last modified Aug. 5, 2016).

2. *Childhood Cancers*, NAT'L CANCER INST., <http://www.cancer.gov/types/childhood-cancers> (last updated Aug. 30, 2017).

3. Duncan, *supra* note 1. Twelve percent of the children diagnosed with cancer this year will not survive. *Id.*

4. *Id.*

5. See Duncan, *supra* note 1; KIDS V CANCER, RESEARCH TO ACCELERATE CURES AND EQUITY FOR CHILDREN ACT (2017), <http://www.kidsvcancer.org/wp-content/uploads/2017/03/RACE-for-Children-Act-ONE-PAGER-.pdf>.

6. *Childhood Cancers Research*, NAT'L CANCER INST., <http://www.cancer.gov/research/areas/childhood> (last updated Mar. 1, 2018).

7. Peter C. Adamson et al., *Drug Discovery in Paediatric Oncology: Roadblocks to Progress*, 11 NATURE REV. CLINICAL ONCOLOGY 732, 732 (2014); see also Holly Fernandez Lynch, *Give Them What They Want? The Permissibility of Pediatric*

Children's Oncology Group ("COG"), has inferred potential negligence by the pharmaceutical companies which continue to brush off the need of pediatric cancer research.⁸

The lack of internal incentives within the pharmaceutical industry entice companies to spend valuable money and time on pediatric research which has left children to be treated as *miniature adults*, when, in reality, they differ immensely.⁹ The vast differences from adults have led to an individualized medical specialty solely dedicated to children called pediatrics.¹⁰ "Pediatric oncology is a medical specialty focused on the care of children with cancer,"¹¹ and has evolved in less than sixty years into its own medical sub-specialty.¹² The pharmaceutical industry has disregarded the differences between children and adults, leaving children to be treated with medication either only approved for or only tested on adults.¹³ Pediatric doctors are forced to prescribe children *off-label* medications that have only been approved for use in adults.¹⁴ These physicians must estimate appropriate, weaker doses for their child patients based on dosages found to be safe in adults, usually using the child's weight as the barometer for comparison.¹⁵ Although this practice is custom within the field, *off-label* use

Placebo-Controlled Trials Under the Best Pharmaceuticals for Children Act, 16 ANNALS HEALTH L. 79, 79 (2007).

8. Adamson et al., *supra* note 7, at 732–33.

In the [United States], approximately 60% of funding for biomedical research stems from the private biopharmaceutical sector. The next largest funder is the [National Institute of Health ("NIH")], which supports approximately 25% of research. For childhood cancers, however, which represent a constellation of more than 100 rare and ultra-rare diseases, the biopharmaceutical sector has an almost negligible investment, resulting in virtually all research funding emanating from the National Cancer Institute ("NCI"), private foundations, and philanthropic sources. This limitation of funding and investment from industry impacts all key areas of drug development, spanning target discovery through clinical development.

Id. at 732 (footnote omitted).

9. Fernandez Lynch, *supra* note 7, at 79. "Despite their similar appearance, children are not just miniature adults. They experience different thought processes, are given different legal rights, and responsibilities . . ." *Id.* (footnote omitted).

10. *Id.*

11. *Childhood Cancers*, *supra* note 2.

12. Adamson et al., *supra* note 7, at 733.

13. Fernandez Lynch, *supra* note 7, at 82; Lisa Jerles, Note, *The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act—Helping or Hurting America's Children?*, 6 CARDOZO PUB. L. POL'Y & ETHICS J. 515, 516–17 (2008).

14. Jerles, *supra* note 13, at 517; *see also* Fernandez Lynch, *supra* note 7, at 82–83.

15. S. Rep. No. 105-43, at 51 (1997); Fernandez Lynch, *supra* note 7, at 83; *see also* Jerles, *supra* note 13, at 516; Zoe Read, *Our Disproportionate Focus on Adult Over Pediatric Cancer Research*, ATLANTIC: HEALTH (Jan. 2, 2013), <http://www.theatlantic.com/health/archive/2013/01/our-disproportionate-focus-on-adult-over-pediatric-cancer-research/266684/>.

of medications can be dangerous, or at the very least ineffective on pediatric patients, due to the uncertainty of particular estimates.¹⁶ This uncertainty may lead physicians to potentially withhold certain medicines that could have provided potential benefits to that child, leading to a possible catastrophic result.¹⁷

Adults diagnosed with cancer may be comforted by the idea that several different treatments may be available to them.¹⁸ On the other hand, children—as well as their families—may not feel the same, as both clinical trials and drugs are not a priority among companies that want to quickly launch effective drugs into the market.¹⁹ Current drug development focuses mainly on cancers that are close to, if not non-existent, in children such as adult carcinomas.²⁰

Since the early 1970s, the federal government has made a more concerted effort to regulate the pediatric field and has attempted to improve the efficacy and safety, as well as increase the number of pharmaceutical drugs available specifically for children.²¹ Within the last ten to fifteen years, the federal government has attempted to improve the market and make more drugs available to treat children, especially through the 2002 Best Pharmaceuticals for Children Act (“BPCA”) and the Pediatric Research Equity Act (“PREA”) of 2003.²² These laws have been incrementally successful, albeit with a *limited positive impact*, “leading to hundreds of drug

16. S. Rep. No. 105-43, at 51; Fernandez Lynch, *supra* note 7, at 82–83; see also I. Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661, 662 (2003).

17. Lynch, *supra* note 7, at 83.

18. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, 535 NATURE INT’L WKLY. J. SCI. 465, 465 (2016), http://www.nature.com/polopoly_fs/1.20331!/menu/main/topColumns/topLeftColumn/pdf/535465b.pdf.

19. *Id.*

20. Adamson et al., *supra* note 7, at 732.

21. Jerles, *supra* note 13, at 515; see also Lauren Hammer Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 135–36 (2003).

22. Jerles, *supra* note 13, at 515–16; Fernandez Lynch, *supra* note 7, at 94–95; *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466; see also Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 1, 115 Stat. 1408, 1408 (codified as amended in scattered sections of 21 U.S.C.); Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 1, 117 Stat. 1936, 1936 (codified as amended in scattered sections of 21 U.S.C.).

labels being updated with information for use in children.”²³ But despite the *limited positive impact* in terms of the entire pediatric pharmaceutical field, there are still not enough drugs being evaluated in children battling cancer and, due to legal loopholes, children fighting cancer have been prevented from access to promising new drugs.²⁴ In response to the modest success of these prior laws, legislation is now attempting to eliminate those exemptions and loopholes to increase opportunities for drug development and change the pediatric cancer landscape for the better.²⁵

The PREA and the BPCA both were enacted roughly fifteen years ago during a time when drugs were developed to fight specific types of cancers in certain parts of the body.²⁶ One barrier to drug development breakthroughs, specifically for pediatric cancer, stands out plain and simple—“adults do not develop pediatric cancers.”²⁷ Additionally, methods for drug development have changed in oncology.²⁸ Instead of targeting specific types of cancers, advances in cancer research have led to drugs being developed through *molecular targeting*.²⁹ Using the exceptions in PREA, companies can get a waiver from the Food and Drug Administration (“FDA”), which does not require conducting pediatric studies for their drugs, thus preventing children with cancer from accessing new drugs.³⁰ New legislation originally proposed to Congress in 2016—and was reintroduced February 27, 2017—will end those exceptions, thus not awarding more waivers to pharmaceutical companies.³¹ This legislation is called the

23. Adamson et al., *supra* note 7, at 737; *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

24. Adamson et al., *supra* note 7, at 737; *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

25. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466; *A RACE to the Finish!*, CHILD. CAUSE FOR CANCER ADVOC. (July 10, 2017), <http://www.childrenscause.org/blog/2017/2/27/a-bill-to-generate-more-treatments-for-childhood-cancer>.

26. Rick Allen, Opinion, *Race Is Now on to Pass the RACE for Children Act to Beat Childhood Cancer*, AUGUSTA CHRON. (Ga.), July 16, 2017, at E3; *see also* § 1, 115 Stat. at 1408; § 1, 117 Stat. at 1936.

27. Allen, *supra* note 26.

28. *Id.*

29. *Id.* The law has not changed or been updated to reflect scientific advances and has thus stifled childhood cancer research and treatment. *Id.*

30. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466; § 2(a), 117 Stat. at 1936–37.

31. *Id.*; Research to Accelerate Cures and Equity for Children Act, S. 456, 115th Cong. §§ 1–2 (as introduced in Senate, Feb. 27, 2017).

Research to Accelerate Cures and Equity for Children Act (“RACE”).³² RACE updates the 2003 PREA law to better correlate to advances in medicine.³³

This Comment will explain the current landscape of pediatric drug development and how scientific advances have caused the need for legislation throughout the past.³⁴ Part II will discuss the history of children in pediatric research and examine how history has influenced the current landscape of pediatrics, especially within pediatric oncology.³⁵ Part III will discuss prior law, the influence of historical actions on the creation of these laws, and how these laws have evolved and adapted since enactment.³⁶ Part IV will discuss the proposed new legislation and how it updates outdated prior law to better reflect advances in modern medicine.³⁷ Lastly, Part V will offer a conclusion.³⁸

II. CHILDREN IN MEDICAL RESEARCH: UNREGULATED RESEARCH TO PARANOIA TO MODERN DAY

There is a long, dark history of abuses when it comes to pediatric research, which have attached a negative connotation to the practice.³⁹ Those abuses of children in medical experimentation caused concern in the latter portion of the twentieth century, creating a *protective attitude*, which has incidentally led to children being virtually excluded from research.⁴⁰ But the progress resulting from clinical research in pediatrics from the 1950s to the late 1990s has contributed to a policy shift favoring participation of children in medical studies.⁴¹ Additionally, the halted—or at best, slowed

32. S. 456 § 1. Also presented to the House of Representatives on the same date as H.R. 1231. *Id.*

33. Michael McCaul et al., *The Race to Fight Childhood Cancer*, HILL (July 12, 2017, 2:30 PM), <http://www.thehill.com/blogs/congress-blog/healthcare/341686-the-race-to-fight-childhood-cancer>.

34. *See infra* Parts I–IV.

35. *See infra* Part II.

36. *See infra* Part III.

37. *See infra* Part IV.

38. *See infra* Part V.

39. Breslow, *supra* note 21, at 135–36.

40. Fernandez Lynch, *supra* note 7, at 86; Michelle Oberman & Joel Frader, *Dying Children and Medical Research: Access to Clinical Trials as Benefit and Burden*, 29 AM. J.L. & MED. 301, 301 (2003).

41. Oberman & Frader, *supra* note 40, at 302–04.

By the mid-1980s, the absence of effective treatment, much less cures, for Acquired Immune Disorder Syndrome (“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.

progress—of potentially valuable biomedical advances due to the many regulations put in place to protect children, had led to many federal policy changes towards the end of the 1990s.⁴² For example, in 1998, the FDA mandated that the NHI supported Phase III clinical trials, which were to be performed to include children, unless there was proper justification for an exclusion.⁴³ The general shift in American thinking in terms of including children in medical research tends to get hazy regarding “participation of children in Phase I clinical trials, which are intended to establish, ‘toxicity, metabolism, absorption, elimination, and other pharmacological action.’”⁴⁴ Although conducting Phase I studies is necessary to benefit sick children in the future, it does not have the necessary weight to solely justify medical experimentation on children.⁴⁵ But the evidence suggests that enrollment in trials *produces better outcomes* compared to non-enrollment, as well as the increased success in later phase trials have led to continued enrollment in Phase I trials, despite the lasting moral dilemma.⁴⁶

A. *The Negative Connotation Attached to Pediatric Studies: The Result of Historical Abuses*

Due to an extensive list of *historical abuses* in research, children have been protected from participation in medical research, thus limiting medical advances in the field.⁴⁷ With little advances in modern day pediatric medicine, in comparison to the advances in adult medicine, this “protective attitude went too far.”⁴⁸ Throughout history, children have been used in medical testing because they were *convenient and cheap subjects*, as they could not safeguard their own rights and interests.⁴⁹ Before the twentieth century, the legal status of a child was not the same as it is today.⁵⁰ Children

Id. at 304 (footnote omitted).

42. *Id.* at 303.

43. *Id.*

44. *Id.* at 304–05 (quoting George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL’Y 297, 310 (1996)). “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.” Oberman & Frader, *supra* note 40, at 305.

45. *Id.* at 305.

46. *See id.* at 307–08.

47. Fernandez Lynch, *supra* note 7, at 86 & n.30.

48. *Id.* at 86; *see also* Read, *supra* note 15.

49. Lanie Friedman Ross & Catherine Walsh, *Minority Children in Pediatric Research*, 29 AM. J.L. & MED. 319, 320 (2003).

50. *See* Breslow, *supra* note 21, at 136.

were considered “chattel, property, and extensions of their parents.”⁵¹ Due to the little recourse the law provided, children were legally unable to protect their own interests, resulting in children being vulnerable to many cases of what would currently be classified as *abuse or abandonment*.⁵²

Many developments from medical testing were results of research performed on orphans, *institutionalized children*, or even the physician’s own children.⁵³ Physicians used the types of children mentioned previously to develop vaccines for diseases, such as: Small pox, measles, *tuberculosis*, *scurvy*, and *ricketts*.⁵⁴ These medical tests involved exposing children to strands of these diseases after inoculation with a potential vaccine.⁵⁵ To determine the efficacy of surgical procedures and medical technology, such as X-rays, physicians used children as experimental test subjects.⁵⁶ Although there was some minor backlash throughout history regarding the use of medical experimentation on children, it was not until after World War II—when the horrific experiments conducted by the Nazis had been publicized—that there was a true focus on protections of research subjects in medical experimentation.⁵⁷ While the subsequent advances in the pediatric field stemmed from medical experimentation and drug testing on children, their vulnerability was exploited until regulations were put into place.⁵⁸

B. *Responses to Medical Abuse of Children*

Public outrage, dated as far back as the 1870s, was a driving factor in the creation of organizations to protect children.⁵⁹ This led the medical community to realize that the needs of children are different from those of adults.⁶⁰ In 1873, a separate division was created by the American Medical Association (“AMA”) to focus solely on women and children.⁶¹ Despite the growing outcry supporting children’s rights and protections, there was not an entity created that would promote children’s welfare until 1930 when the independent American Academy of Pediatrics was founded.⁶² In addition to children, other classes of people, including African Americans and the

51. *Id.*

52. *Id.*

53. *Id.* at 136–37.

54. *Id.* at 137.

55. Breslow, *supra* note 21, at 137.

56. *Id.* at 138.

57. *See* Cohen, *supra* note 16, at 673; Ross & Walsh, *supra* note 49, at 320.

58. Breslow, *supra* note 21, at 137.

59. *Id.* at 136.

60. *Id.*

61. *Id.* at 136–37.

62. *Id.* at 137.

elderly, were subjected to medical experimentation due to their vulnerability.⁶³ Public exposure of the abuse occurring in the medical field prompted enough backlash to fuel legal regulation of clinical studies.⁶⁴

In response to the Holocaust and the Nazi's medical practices, after World War II, the first international code establishing rights for human research subjects was created and titled the Nuremberg Code ("Code").⁶⁵ The Code did not allow research on non-consenting persons, employing the doctrine of informed consent, a principle still practiced today.⁶⁶ Although by this time it was established that children could not consent themselves, the Code highlighted informed consent of competent individuals and not incompetent subjects.⁶⁷ It was not addressed until 1964, when the World Medical Association published the Declaration of Helsinki, which included guidelines for *surrogate consent* for those who could not consent themselves.⁶⁸ Although these international guidelines were established, they were simply guidelines—lacking any legitimate legal authority to bind the science community.⁶⁹

Until the 1970s, the government did not take many steps towards regulating pediatric testing, including not codifying any of the earlier international guidelines published in years prior.⁷⁰ In 1973, the federal government finally responded to children's need for clinical protections in medical research when "the Department of Health, Education, and Welfare—now the Department of Health and Human Services ("HHS")"—issued new rules on experimentation with human subjects.⁷¹ Children did not benefit from these rules as a majority of the focus was placed on adult subjects.⁷² Responding to this lack of focus on children and to create legal standards for testing in children, "Congress enacted the National Research Act, which [generated] the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission")."⁷³ But

63. Breslow, *supra* note 21, at 138.

64. *Id.*

65. Fernandez Lynch, *supra* note 7, at 98; Joanne Roman, Note, *U.S. Medical Research in the Developing World: Ignoring Nuremberg*, 11 CORNELL J.L. & PUB. POL'Y 441, 448 (2002).

66. 45 C.F.R. § 46.116 (2016); Fernandez Lynch, *supra* note 7, at 98; Roman, *supra* note 65, at 445, 448–49.

67. Fernandez Lynch, *supra* note 7, at 98.

68. *Id.*

69. *Id.*

70. See Breslow, *supra* note 21, at 138; Fernandez Lynch, *supra* note 7, at 98–99.

71. Breslow, *supra* note 21, at 138; Fernandez Lynch, *supra* note 7, at 99.

72. Breslow, *supra* note 21, at 138.

73. *Id.*

the National Commission did not submit any “recommendations for pediatric clinical standards” for roughly four years.⁷⁴ The rules were finally published in 1983 and created strict guidelines protecting child clinical subjects tested in HHS funded research.⁷⁵ The rules only applied to HHS funded research—limiting the reach of legal authority.⁷⁶ There was no change to the application of these rules until 2000, through the Children’s Health Act of 2000, that Congress mandated the HHS to create rules for the general testing of children, both in public and privately funded clinical studies.⁷⁷

Following the history of abuse, federal regulations that were put into place to safeguard children from similar harm have led to the current landscape where pediatric testing and drugs developed solely for children are *virtually non-existent*.⁷⁸ In less than fifty years, clinical research in pediatric oncology has made substantial progress against many forms of childhood cancer.⁷⁹ Although overall progress has been limited, “[s]uch 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.”⁸⁰ But due to several factors, such as the strict regulations protecting children, the pediatric field is much more complicated than working with adults—and pharmaceutical companies could avoid the challenges of working with pediatric patients by choosing not to perform pediatric studies.⁸¹ Actions like these by pharmaceutical companies exemplify children’s need for legislative action to be included in mainstream pharmaceutical research.⁸²

Due to pharmaceutical companies’ exclusion of marketing or labeling drugs for pediatric populations—leading to a lack of pediatric drugs on the market—children have been labeled as *therapeutic orphans*, as they are forced to use treatment designed for adults instead of treatments designed for themselves.⁸³ Pediatricians have been forced to treat children through

74. *Id.* at 139.

75. *Id.*

76. *See id.* at 139–40.

77. Breslow, *supra* note 21, at 139–40; *see also* 42 U.S.C. § 284 (2000).

78. Fernandez Lynch, *supra* note 7, at 86; Oberman & Frader, *supra* note 40, at 301–02.

79. Oberman & Frader, *supra* note 40, at 302. “The most common form of childhood leukemia went from being a nearly always fatal disease to one cured more than [75%] of the time.” *Id.*

80. *Id.* “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.” *Id.*

81. Breslow, *supra* note 21, at 144; Lynch, *supra* note 7, at 86.

82. Breslow, *supra* note 21, at 144.

83. *Id.* at 145.

'off-label' prescribing of medicines labeled for adults with the same or similar condition.⁸⁴ In an effort to improve drug labeling for pediatric use, the FDA published a *final rule* in 1994, which did not require any new testing, but required pharmaceutical companies to examine available drug data on pediatric use.⁸⁵ If information was found to support pediatric labeling for the drug, then a condition required that company to file a supplemental new drug application.⁸⁶ In order to satisfy the pediatric labeling requirement, this rule allowed "pharmaceutical companies [to] use *adequate and well-controlled* adult studies in addition to pharmacokinetic, safety, and pharmacodynamic[s] data" as support.⁸⁷ Despite an attempt to change the landscape of pediatric medicine, this FDA initiative failed to encourage pharmaceutical companies to conduct any pediatric research or improve pediatric labeling.⁸⁸

The failure of the 1994 voluntary rule led the FDA to publish a much more stringent regulation in 1998, the Pediatric Rule ("Pediatric Rule").⁸⁹ This rule awarded the FDA with the authority to require pharmaceutical companies to conduct pediatric studies on new and existing marketed drugs.⁹⁰ However, the Pediatric Rule was invalidated by a United States district court in *Association of American, Physicians & Surgeons v. FDA*.⁹¹ The court granted the plaintiff's motion for summary judgment and held that the "Pediatric Rule exceed[ed] the FDA's statutory authority."⁹²

84. *Id.*

85. Breslow, *supra* note 21, at 151–52; *see also* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. 64,240, 64,240 (1994) (codified as amended in 21 C.F.R. § 201 (2016)).

86. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Breslow, *supra* note 21, at 152; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. at 64, 240.

87. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. at 64,240.

88. Breslow, *supra* note 21, at 152–53; Fernandez Lynch, *supra* note 7, at 92–93.

89. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,632 (1998) (codified as amended in 21 C.F.R. §§ 312, 314 (1998)); *Ass'n of Am., Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204, 205 (D.C. Cir. 2002).

90. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. at 66,632.

91. 226 F. Supp. 2d 204, 222 (D.C. Cir. 2002).

92. *Id.*

This court does not pass judgment on the merits of the FDA's regulatory scheme. The Pediatric Rule may well be a better policy tool than the one enacted by Congress; it might reflect the most thoughtful, reasoned, balanced solution to a

Before the Pediatric Rule was finalized, the failures of the FDA to improve the pediatric landscape prompted Congress to intervene with the Food and Drug Administration Modernization Act of 1997 (“FDAMA”), which provides drug manufacturers economic incentives for performing pediatric drug studies.⁹³ One of the most influential economic incentives was contained in section 111 of the FDAMA, the BPCA, which was codified as the pediatric exclusivity provision.⁹⁴ The BPCA exclusivity provision was targeted to improve pediatric labeling by dangling an economic incentive in the form of a six-month extension to a drug manufacturer’s patent or exclusivity period in exchange for the manufacturer testing the drug in a pediatric study.⁹⁵ Although the provision did not require pediatric testing, it was considered a success despite being riddled with limitations.⁹⁶ These limitations included: The *voluntary* participation by companies—the provision only affected companies which *had drugs on patent* or were in an *exclusivity term* at that particular point in time—and the provision was only established to last for five years.⁹⁷ Despite these limitations, the exclusivity provision helped incentivize pediatric research leading to the BPCA’s re-enactment in 2002.⁹⁸ The BPCA became even more important to the FDA after the Pediatric Rule was struck, as it was the FDA’s only remaining means of directing a change in the pediatric landscape.⁹⁹

C. *Pediatric Involvement in Clinical Studies for Childhood Cancer*

Prior to the 1990s, the regulations put into place to protect children led to a small number of enrollees into pediatric oncology clinical trials.¹⁰⁰ Since the early 2000s, this has not been the case as a large majority of children fighting cancer in the United States enroll in Phase III clinical trials,

vexing public health problem. The issue here is not the Rule’s wisdom. Indeed, if that were the issue, this court would be a poor arbiter indeed. The issue is the Rule’s statutory authority, and it is this that the court finds lacking.

Id.

93. Breslow, *supra* note 21, at 153–55, 157 n.213; *see also* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305-09 (codified as amended in scattered sections of 21 U.S.C.).

94. *See* 21 U.S.C. § 355c (2012); § 111, 111 Stat. at 2306–07; Breslow, *supra* note 21, at 173–74.

95. 21 U.S.C. § 355c (b)–(c); Breslow, *supra* note 21, at 156 n.201, 173–74.

96. *See* Breslow, *supra* note 21, at 154.

97. *See id.* at 154–55, 156 n.201.

98. *See* Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 3, 115 Stat. 1408, 1408 (codified as amended in scattered sections of 21 U.S.C.); Breslow, *supra* note 21, at 162.

99. Cohen, *supra* note 16, at 661 (emphasis in original).

100. Oberman & Frader, *supra* note 40, at 301.

which are experimental treatments.¹⁰¹ A majority of children with cancer become an experimental subject compared to a small minority of adults, signifying a lack of concrete medical options for children battling cancer.¹⁰² Until the 1960s, there was *no effective* treatment that children suffering from this *life-threatening disease*[] could look towards for help.¹⁰³ Around that time, it had become apparent that in order to save children’s lives, clinical studies were required, but at the same time, regulations to safeguard children were being put in place.¹⁰⁴

“In less than half of a century,” clinical studies and pediatric cancer research combined to make great strides in the pediatric oncology field.¹⁰⁵ The success of these studies helped turn the tide in American thinking to allowing children to partake in medical studies.¹⁰⁶ Progress in treatment development for Human Immunodeficiency Virus (“HIV”) and cancer have particularly led the way in transforming the perception of children partaking in medical studies.¹⁰⁷ But despite the medical progress, there have been some societal conflicts regarding children partaking in clinical trials, especially Phase I trials.¹⁰⁸ Phase I clinical trials are used to determine, “toxicity, metabolism, absorption, elimination, and other pharmacological action.”¹⁰⁹ The purpose behind a Phase I study is not for therapeutic benefit; all benefits are *incidental, or indeed coincidental*, because its essential use is to “determine the maximum dose at which the drug can safely be tolerated.”¹¹⁰

An issue present in treating children is the fact that introducing new treatments for children requires pediatric subjects be put through clinical trials—Phase I, II, and III—as rigorous as those for adults.¹¹¹ “Children differ physiologically from adults,” so the data learned through an adult trial can be useless and even dangerous for pediatric use.¹¹² In order to benefit

101. *Id.*

102. *Id.* at 302.

103. *Id.*

104. *Id.*

105. Oberman & Frader, *supra* note 40, at 302.

106. *Id.*

107. *Id.* at 304.

108. *Id.* at 304–05.

109. George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL’Y 297, 310 (1996) (quoting PRESIDENT’S COMM’N FOR THE STUDY OF ETHICAL PROBLEMS IN MED. & BIOMEDICAL & BEHAVIORAL RESEARCH, PROTECTING HUMAN SUBJECTS 64 (1981)). Phase II studies follow Phase I studies and are focused on *safety and biological effects*. Oberman & Frader, *supra* note 40, at 308.

110. Oberman & Frader, *supra* note 40, at 305.

111. *Id.*

112. *Id.*

future patients and continue to make progress, these studies are necessary, but even this future benefit cannot be the sole justification for subjecting these children to clinical experimentation.¹¹³ But, children in Phase I studies are extremely ill, and have not responded to standard treatment, so these patients volunteer for these trials because the patient and/or their family “naturally view research as their best chance [for] survival.”¹¹⁴ This is called *therapeutic misconception*.¹¹⁵ The desperation to find a cure drives a sick patient to believe that Phase I clinical trials constitute a *treatment* more than a non-therapeutic medical experimentation.¹¹⁶

Tension in conducting Phase I clinical trials challenges every party attempting to protect the child’s best interest.¹¹⁷ As a minor, a child is not legally autonomous and cannot consent to their own healthcare, especially to enroll themselves into clinical trials.¹¹⁸ The child’s guardian(s), usually parents, must authorize enrollment into these trials.¹¹⁹ Another issue present in a child’s enrollment into a Phase I trial involves the parent’s decision to enroll a terminally ill child into a clinical study.¹²⁰ A parent may not have the *best interests* of the child in mind when faced with such a decision.¹²¹ Parents of a terminally ill child may have an *unrealistic hope* that the child will improve despite the disease or “may consent to research in an effort to obtain a sense of control over” the death of their child.¹²² With our interest in safeguarding a child’s best interest, it might never be possible to have a *rational justification* for Phase I research with children, but these studies must always continue with the best interest of the child in mind.¹²³

113. *Id.*

114. *Id.* at 306, 308–09. “One survey of clinical researchers found that [ninety-four percent] agreed that adult patients enroll in Phase I studies ‘mostly for the possible medical benefit.’” Oberman & Frader, *supra* note 40, at 309 (quoting Eric Kodish et al., *Ethical Issues in Phase I Oncology Research: A Comparison of Investigators and Institutional Review Board Chairpersons*, 10 J. CLINICAL ONCOLOGY 1810, 1812 (1992)).

115. *Id.* at 308.

116. *Id.*

117. *See id.*

118. *Id.* at 314.

119. Oberman & Frader, *supra* note 40, at 314. “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.” *Id.* at 315.

120. *See id.* at 314–15.

121. *See id.* at 315.

122. *Id.* at 315.

123. Oberman & Frader, *supra* note 40, at 317.

III. THE CARROT AND STICK APPROACH: THE FDA'S TANDEM SYSTEM DESIGNED TO CHANGE THE LANDSCAPE OF PEDIATRIC MEDICINE

Costs of clinical trials, especially those in pediatrics, continue to rise and without legislation in place to act as an *incentivizing device*, pharmaceutical companies would have little economic interest in pursuing pediatric trials.¹²⁴ Currently, many companies will typically pursue pediatric use in a developing adult drug, which if it has shown promise in children, is because of the *carrot or [the] stick*.¹²⁵ The Pediatric Rule and FDAMA were the original stick and carrot meant to ensure drugs would be tested in children.¹²⁶ But statutory issues leading to the suspension of the Pediatric Rule and limitations embedded in the FDAMA's exclusivity provision led to legislative changes in the early 2000s.¹²⁷

The BPCA of 2002—reauthorized in 2007—provides drug companies with “an additional six months of marketing exclusivity [for their] patented drug” in exchange for conducting an FDA-requested pediatric study.¹²⁸ The reward-based arrangement provided an incentive for pharmaceutical companies to test their drugs on pediatric populations, thus the *carrot* of the modern day regulatory system for pediatric research.¹²⁹

The PREA of 2003—also reauthorized in 2007—authorizes the FDA with the ability to force testing of new drugs in a pediatric population by the drug manufacturer.¹³⁰ This law awarded the FDA with the power to require pediatric testing of drugs already in the market stream, as well as drugs not yet approved by the FDA.¹³¹ The BPCA was created to increase information available about the use of drugs in children through economic incentives, and

124. Jerles, *supra* note 13, at 526–27.

125. Megan Scudellari, *The Kids Aren't All Right: The Number of Children Dying of Cancer Is Climbing, Yet New Medications to Treat Them Are Aching Scarce*, NEWSWEEK, Aug. 7, 2015, at 44, 46.

126. Ross & Walsh, *supra* note 49, at 322.

127. See Breslow, *supra* note 21, at 162; Ross & Walsh, *supra* note 49, at 322–23.

128. Scudellari, *supra* note 125, at 46. “For a drug that earns \$1 billion per year, that’s an extra \$500 million [a company could earn] for a pediatric study that will cost a fraction of that.” *Id.* It provides an economic incentive for pharmaceutical companies. See Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 10, 115 Stat. 1408, 1415 (codified as amended on scattered sections of 21 U.S.C.); Scudellari, *supra* note 125, at 46.

129. Fernandez Lynch, *supra* note 7, at 94.

130. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 505B(a)(2), 117 Stat. 1936, 1936 (codified as amended in scattered sections of 21 U.S.C.); Scudellari, *supra* note 125, at 46.

131. Fernandez Lynch, *supra* note 7, at 95; Jerles, *supra* note 13, at 521.

the PREA's mandate for pediatric testing supports that vision, providing "the stick to the BPCA's carrot."¹³²

A. *The Incentive-Based "Carrot": The Best Pharmaceuticals for Children Act*

The expiration of the FDAMA in 2001 led to the enactment of the BPCA in 2002.¹³³ A lack of prescriptions being tested and approved for use in children, as well as dosing adult medication to children based solely on weight, led Congress to intervene.¹³⁴ Additionally, because drugs were designed with adults in mind, the absence of *age-appropriate formulations* and devices for use were causing difficulties among pediatric patients.¹³⁵ Congress enacted the BPCA upon a finding that the exclusivity provision of the FDAMA had positively impacted the pediatric population unlike any legislation prior.¹³⁶

BPCA of 2002 continued the goal of the FDAMA but made some alterations, such as eliminating the Pediatric List which did not meet its intended goal of effectively prioritizing the certain drugs that should have been tested in children.¹³⁷ Although pediatric testing is not required and remains voluntary, the 2002 BPCA set a two-level system in place where the FDA researches current drugs to determine if it may produce a benefit to pediatric populations.¹³⁸ If the FDA were to find a drug that shows potential to produce benefits to pediatric populations, the FDA will send a written request to the patent holder to perform a pediatric clinical study with its drug.¹³⁹ If the patent holding company decides to perform the requested pediatric clinical trials centered around its own drug, it would earn an additional six-month term of market exclusivity.¹⁴⁰ This additional six months of market exclusivity acts as an incentive for these companies to perform pediatric studies.¹⁴¹ But due to the voluntary nature of the statute, a patent holder can choose not to perform the requested pediatric clinical

132. Fernandez Lynch, *supra* note 7, at 95.

133. § 1, 115 Stat. at 1408; Jerles, *supra* note 13, at 517.

134. Jerles, *supra* note 13, at 516.

135. *Id.* at 517, 527.

136. *Id.* at 517. "The BPCA increases the capacity of the FDA, enabling it to handle its new role as the initiator and arbitrator of pediatric studies—something that the original bill had failed to do." Breslow, *supra* note 21, at 178.

137. Jerles, *supra* note 13, at 518.

138. Breslow, *supra* note 21, at 134.

139. Jerles, *supra* note 13, at 518.

140. Breslow, *supra* note 21, at 134; Jerles, *supra* note 13, at 518.

141. Jerles, *supra* note 13, at 518.

study.¹⁴² If the patent holder opts not to perform the requested study, the statute allows the FDA to contract out of the drug testing, with entities that have pediatric clinical trial expertise, such as universities and hospitals.¹⁴³

Additionally, a significant addition to the BPCA of 2002 was the creation of a program to test off-patent drugs, which the FDAMA lacked prior.¹⁴⁴ This reform was called the Program for Pediatric Studies of Drugs Lacking Exclusivity (“Program”).¹⁴⁵ This Program called for the FDA and NIH to work together to develop a list of *off-patent or off-exclusivity* drugs that show potential to produce a benefit to the pediatric populations.¹⁴⁶ Under the BPCA, the FDA may issue written requests to the application holders of a drug that is deemed to require more research.¹⁴⁷ If the application holders do not respond within thirty days of the request, or choose not to conduct the requested pediatric trials with the drug, the FDA can then publish requests for proposals from entities with pediatric clinical trial expertise.¹⁴⁸

The BPCA of 2002 also requires that any pediatric report, conducted pursuant to a written request for a clinical trial, must be published in the Federal Register within 180 days after it has been submitted to the FDA.¹⁴⁹ Additionally, in response to lack of pediatric labeling, the BPCA awards the FDA the power to deem a drug mislabeled.¹⁵⁰ When the drug manufacturer refuses to accept the FDA’s decision for a labeling change, the BPCA allows the FDA to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act.¹⁵¹ Lastly, due to the unease from the pediatric oncologist community, the BPCA attempts to increase research performed in their field which despite the exclusivity provision, was markedly absent.¹⁵² This attempt culminated in the creation of a Pediatric Subcommittee of the Oncologic Drugs Advisory Committee to evaluate cancer drugs and prioritize which would be of the most use for children.¹⁵³ Though the

142. Breslow, *supra* note 21, at 134.

143. *Id.*; Jerles, *supra* note 13, at 518.

144. Breslow, *supra* note 21, at 174–76.

145. *Id.* at 174; *see also* 42 U.S.C. § 284 (2012).

146. 42 U.S.C. § 284(a) (2012); Breslow, *supra* note 21, at 174.

147. 42 U.S.C. § 284(c) (2012); Breslow, *supra* note 21, at 174.

148. 42 U.S.C. § 284(c)(3) (2012). Once a drug application holder has declined to conduct a test or misses the thirty-day deadline, it is not eligible to respond to a written request for a contract from the FDA. *Id.* § 284(c)(4).

149. Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 9, 115 Stat. 1408, 1415 (codified as amended in scattered sections of 21 U.S.C.); Breslow, *supra* note 21, at 175.

150. § 3, 115 Stat. at 1408; Breslow, *supra* note 21, at 175.

151. 42 U.S.C. § 284(c)(10)–(11) (2012); Breslow, *supra* note 21, at 175.

152. Breslow, *supra* note 21, at 178.

153. *Id.*

participation under BPCA is voluntary and in the control of the pharmaceutical companies, the BPCA attempts to compensate for the voluntary nature by including programs, such as the Pediatric Studies Program or the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, which will help facilitate and begin research drugs that are not researched by the pharmaceutical companies.¹⁵⁴

B. *The Pediatric Research Equity Act: The “Stick” to the BPCA’s “Carrot”*

The purpose of the BPCA of 2002 was to increase the amount of research on drugs that children were using due to the lack of labeling and dosages.¹⁵⁵ Despite the success of the earlier exclusivity provision, Congress believed that the voluntary testing established under the BPCA was not adequate and thought the FDA needed the requisite authority to mandate pediatric testing.¹⁵⁶ Additionally, the Pediatric Rule had just been invalidated by a United States District Court in 2002, which held that the Rule exceeded the FDA’s statutory authority.¹⁵⁷ Due to the importance of proper labeling of pediatric drugs and Congress’ belief that the FDA needed the authority to mandate pediatric testing, Congress enacted the Pediatric Research Equity Act of 2003.¹⁵⁸

The PREA of 2003 gave the FDA the authority to require pediatric testing of drugs already present in the market as well as mandating pediatric testing and labeling on all drugs that have not been approved by the FDA.¹⁵⁹ This enactment was meant to be non-voluntary support for the voluntary exclusivity provision within its sister statute, the BPCA of 2002.¹⁶⁰ The PREA of 2003 mandates that pharmaceutical companies must, when submitting a new drug application, submit sufficient information regarding the clinical indication of the drug in *relevant pediatric subpopulations*, even if the drug was not intended for pediatric use.¹⁶¹ Additionally, this statute

154. *Id.* at 181–82.

155. *See* § 3, 115 Stat. at 1408–09; Breslow, *supra* note 21, at 146; Jerles, *supra* note 13, at 520–21.

156. Jerles, *supra* note 13, at 520.

157. *Ass’n of Am., Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204, 222 (D.C. Cir. 2002).

158. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 1, 117 Stat. 1936, 1936 (codified as amended in scattered sections of 21 U.S.C.); Jerles, *supra* note 13, at 521.

159. § 2, 117 Stat. at 1936–39; Fernandez Lynch, *supra* note 7, at 95; Jerles, *supra* note 13, at 521.

160. Fernandez Lynch, *supra* note 7, at 94–95.

161. § 2, 117 Stat. at 1936; Fernandez Lynch, *supra* note 7, at 95–96.

mandates drug manufacturers to submit data supporting use in “pediatric subpopulations in which the drug is found to be safe and effective.”¹⁶²

Furthermore, the PREA allows the FDA to require the drug manufacturers to produce sufficient data supporting use in pediatric subpopulations for drugs already approved and actively on the open market.¹⁶³ Because these drugs are already approved, they do not fall under the same classification as a new drug application.¹⁶⁴ Despite receiving authority to require data for existing drugs, the FDA could only mandate the drug manufacturer to conduct pediatric testing after requesting the manufacturer to voluntarily conduct the research.¹⁶⁵ The FDA has the authority to require pediatric data for existing drugs if the drug is used substantially among pediatric populations for the designated use on the label, or if there is the possibility the drug could provide an upgraded therapeutic benefit over the drugs being used for pediatric patients at that time.¹⁶⁶ Additionally, the FDA must show that the absence of proper labeling could create substantial risks for the pediatric population.¹⁶⁷ Similar to the procedure for new drugs yet to be approved, if the drug manufacturer agreed to conduct the research voluntarily, the manufacturer was awarded the additional six months of market or patent exclusivity pursuant to BPCA of 2002.¹⁶⁸ If the manufacturer refused to conduct the pediatric research regarding the drug, the FDA would then refer the study to the Foundation for the National Institute of Health and proceed to contract the study out to an entity with pediatric clinical trial expertise.¹⁶⁹

C. *Results Following BPCA 2002 and PREA 2003: The Reenactment of the Carrot and Stick Approach*

The complexity of conducting childhood studies places barriers around the field, discouraging drug manufacturers from aiming their products at a pediatric audience.¹⁷⁰ Economically speaking, the manufacturer sees no reason to change the current system, which allows pediatricians to prescribe drugs off-label.¹⁷¹ In economic terms, a drug manufacturer can save money without expending additional effort by continuing to target adult

162. Fernandez Lynch, *supra* note 7, at 96 (citing § 2, 117 Stat. at 1936).

163. *Id.* at 95–96; *see also* § 2, 117 Stat. at 1936–37.

164. Fernandez Lynch, *supra* note 7, at 95–96, 96 n.102.

165. Jerles, *supra* note 13, at 522.

166. Fernandez Lynch, *supra* note 7, at 96.

167. § 2, 117 Stat. at 1938; Fernandez Lynch, *supra* note 7, at 96–97.

168. Jerles, *supra* note 13, at 518, 522.

169. *Id.* at 518.

170. *Id.* at 526.

171. *Id.*

use, choosing not to conduct voluntary pediatric clinical studies, and allowing the doctors to keep prescribing drugs off-label.¹⁷² Additionally, due to some problems in BPCA 2002 and PREA 2003, pharmaceutical companies did not have very much difficulty avoiding these regulations.¹⁷³ While these laws pursued improvement and increased availability of drugs to children, both had some negative results in the areas that were designated for upgrades.¹⁷⁴

Companies would manipulate BPCA 2002 and PREA 2003 to their advantage, using several loopholes—riddling these laws.¹⁷⁵ Clinical trial testing takes a very long time to complete; therefore, results do not occur quickly.¹⁷⁶ Both of these laws were enacted for such a short time, thus drug manufacturers would take advantage of the length needed for a clinical trial and delay testing with the hopes of the legislation expiring.¹⁷⁷ Furthermore, shortly before the expiration of their patent—sometimes days—a drug manufacturer could submit data from pediatric testing.¹⁷⁸ In addition to filing a last second application, the FDA was required to review the results within ninety days, giving drug companies a *de facto* three month exclusivity period, even if inadequate testing was performed.¹⁷⁹ Even if the FDA rejects an inadequate study, the drug company is awarded an additional three months of exclusivity for their drug, making a profit at the expense of pediatric studies.¹⁸⁰

Pediatric care requires a completely different mindset than adult care, ranging from the devices used for application of the drug to the way children metabolize drugs.¹⁸¹ Although it is looked at as the cheap alternative by pediatricians, it is practical to prescribe off-label drugs to children, but for many drugs to work properly, they must be re-sized to suit application in children and not adults.¹⁸² Even though these laws were perforated with problems, since enactment, they have helped change the

172. *Id.*

173. Jerles, *supra* note 13, at 526–27.

174. *Id.* at 527.

175. *Id.*

176. *Id.* at 526.

177. *Id.* Drug manufacturers who had begun clinical trials also took advantage of the length needed to complete a trial. Jerles, *supra* note 13, at 526. Clinical trials likely require longer than four years to complete, but the laws only mandated testing for four years. *Id.*

178. *Id.* at 527.

179. *Id.*

180. *Id.*

181. Jerles, *supra* note 13, at 516–17, 527.

182. *Id.* at 527.

perception of children in the medical field in a much more positive light.¹⁸³ Despite many pharmaceutical companies taking advantage of the many loopholes within these laws, the motivation of patent extensions to seek approval for pediatric use was a step in the right direction.¹⁸⁴

Although there were steps taken in the right direction, as well as an increased availability of clinical studies for children, there was very little advancement regarding the development of drugs specifically for use in children.¹⁸⁵ Drug companies test already developed drugs on pediatric subjects, typically recruiting pediatric patients for general tests conducted on everyone afflicted by a certain condition and not just on children.¹⁸⁶ By testing the effects of drugs already approved for adults, pharmaceutical companies still receive the benefit of an additional six months of market exclusivity—giving them “little incentive to develop [new] drugs specifically for” use in pediatric populations.¹⁸⁷ Although the legislation was made in an effort to update labeling of existing drugs and to develop an increased number of new drugs for pediatric patients, these laws “incentivize[] [drug] manufacturers to test drugs already approved for adults, rather than develop new drugs for children,” because it is much less profitable.¹⁸⁸ This has led to a large increase in therapies available to children, but with little increase in drugs developed specifically for use in children.¹⁸⁹ Additionally, when testing drugs on children, drug manufacturers have typically used more cost-cutting methods.¹⁹⁰ When conducting a clinical trial on adult drugs, a company’s first step is usually to study the absorption of a particular drug and how it is metabolized before effectiveness is tested.¹⁹¹ But in order to cut costs of pediatric clinical trials, these drug manufacturers combine both testing for absorption and effectiveness, leading to trials that drag on causing pediatric patients to deny enrollment.¹⁹²

Another issue present within these laws deals with the lack of negative data disclosure from clinical trials.¹⁹³ Different journals of medicine created either voluntary databases to input results, or started to require trials registered with the public clinical trial registry to be published

183. *Id.* at 527–28.

184. *Id.* at 528.

185. *Id.* at 531.

186. Jerles, *supra* note 13, at 530–31.

187. *Id.* at 531.

188. *Id.* at 532.

189. *Id.*

190. *Id.* at 542.

191. Jerles, *supra* note 13, at 542–43.

192. *Id.* at 543.

193. *Id.* at 539.

in that journal.¹⁹⁴ The Fair Access to Clinical Trials Act (“FACT Act”) was introduced in 2005 for the FDA to expand the existing database to make clinical results more readily available to the public.¹⁹⁵ Under the FACT Act, results of both publicly and privately funded clinical trials would be published, despite the results.¹⁹⁶ In 2006, a modified version of the FACT Act was introduced, the Enhancing Drug Safety and Innovation Act.¹⁹⁷ This limited what was published, and no longer required devices or procedures to be published—only detailed information regarding the drug and its approval status.¹⁹⁸ Neither of these bills passed, and were deferred to the Senate Committee on Health, Education, Labor, and Pensions.¹⁹⁹

1. Revival: The Reenactment of the “Carrot and Stick”

Despite having several problems, both acts were reauthorized upon their expiration in 2007.²⁰⁰ Both were reenacted for another five years as part of larger legislation, the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).²⁰¹ The FDAAA helped close some of the existing loopholes and fix other issues which were taken advantage of by pharmaceutical companies.²⁰² Also, an important addition to this act helped pave the way for age-appropriate devices for application of adult drugs in children, with the Medical Device Safety and Improvement Act of 2007.²⁰³ This Act curtails off of the incentive driven attitude of the BPCA, and provides incentives in exchange for the creation of products that children can use for treatments.²⁰⁴ Along with providing incentives for creating products for children, the Act requires that companies pursuing approval for a device have to include *description[s] of . . . pediatric subpopulations* which are afflicted by the issue the device is aimed to fix.²⁰⁵ Further, the Act inspired pediatric device research because within 180 days of enactment, the FDA

194. *Id.*

195. *Id.* at 539–40; *see also* Fair Access to Clinical Trials Act of 2005, S. 470, 109th Cong. § 2(1)–(4)(2005).

196. Jerles, *supra* note 13, at 540.

197. *Id.* at 541; *see also* Enhancing Drug Safety and Innovation Act of 2006, S. 3807, 109th Cong. § 1 (2006).

198. Jerles, *supra* note 13, at 541.

199. *Id.* at 542.

200. *Id.* at 516.

201. *Id.*; *see also* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1, 121 Stat. 823, 823 (codified as amended in scattered sections of 21 U.S.C.).

202. *See* Jerles, *supra* note 13, at 544.

203. *See* § 301-07, 121 Stat. at 859–66; Jerles, *supra* note 13, at 516.

204. *See* § 301-07, 121 Stat. at 859–66; Jerles, *supra* note 13, at 516.

205. § 302, 121 Stat. at 859.

was required to publish a pediatric device research agenda which was to be followed in the development stage.²⁰⁶

a. *The BPCA of 2007*

The FDAAA of 2007 enacted the BPCA of 2007, a reenactment of the BPCA 2002, with some adjustments.²⁰⁷ One major issue BPCA of 2007 was targeted to fix was the situation where pharmaceutical companies could submit pediatric test results, immediately before the patent expired, to attempt to receive patent exclusivity for a maximum of nine months or minimum of three months.²⁰⁸ BPCA 2007, with the intentions of improving the pediatric landscape, aimed to close this loophole by not only removing the period of exclusivity during the FDA's review, but also doubling the time of review from ninety days to 180 days, awarding the FDA much more time to analyze the results provided.²⁰⁹ This effectively removed the ability of pharmaceutical companies to provide inadequate pediatric testing yet reap the benefits of up to nine extra months of exclusivity, three for those companies who provided extremely inadequate pediatric testing.²¹⁰

b. *The PREA of 2007*

Like the BPCA of 2007, the FDAAA of 2007 enacted the PREA of 2007, which reenacted the PREA of 2003.²¹¹ The PREA of 2007 was designed to make some changes to the prior law.²¹² The law removed the requirement that the FDA request a pharmaceutical company to conduct pediatric tests voluntarily before having the authority to mandate testing.²¹³ Without that nuance, the FDA was granted the authority to mandate pediatric testing by pharmaceutical companies, thus avoiding the unnecessary steps

206. § 304, 121 Stat. at 863.

207. Best Pharmaceuticals for Children Act of 2007, Pub. L. No. 110-85, § 501-02, 121 Stat. 876, 876 (codified as amended in scattered sections of 21 U.S.C.).

208. See § 505A, 121 Stat. at 877; Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 3, 115 Stat. 1408, 1408–10 (codified as amended in scattered sections of 21 U.S.C.). Under BPCA 2002, pharmaceutical companies could send inadequate pediatric data to the FDA and reap the benefits of a de-facto exclusivity period while the FDA reviewed the findings, thus taking advantage of the law in place. See § 3, 115 Stat. at 1408–10.

209. Jerles, *supra* note 13, at 519; see also § 505, 121 Stat. at 879.

210. Jerles, *supra* note 13, at 519–20.

211. *Id.* at 519, 522; see also Pediatric Research Equity Act of 2007, Pub. L. No. 110-85, § 402, 121 Stat. 866, 866 (codified as amended in scattered sections of 21 U.S.C.).

212. Jerles, *supra* note 13, at 522; see also § 402, 121 Stat. at 869.

213. Jerles, *supra* note 13, at 522; see also § 402, 121 Stat. at 869.

which delayed progress.²¹⁴ Two major requirements added to the PREA of 2007 helped to improve the landscape of pediatric medicine and increased the FDA's power to mandate testing.²¹⁵ First, the PREA of 2007 required pharmaceutical companies to provide more detailed data in support of a waiver requesting permission for pediatric testing of their drug.²¹⁶ Second, the law requires the FDA to assess the effectiveness of the law through conducting studies with the Institute of Medicine and the Government Accountability Office years after the law, which will help the FDA formulate a plan of attack for the future.²¹⁷

IV. RACE: THE RESEARCH TO ACCELERATE CURES AND EQUITY FOR CHILDREN ACT

As previously mentioned, pediatric cancer is the number one killer among children.²¹⁸ Very little is known about childhood cancers, as the types of cancers and biology of childhood cancers are much different from adult cancers.²¹⁹ PREA and BPCA were enacted first in 2003 and then reenacted in 2007 to increase pediatric research to develop drugs specifically for use in children.²²⁰ The "BPCA ha[d] worked reasonably well for drugs with [a] large market" for use, but still remains voluntary, and does not support drugs for smaller markets, such as cancer.²²¹ Almost every single instance under PREA, cancer drugs that have already been developed for adults receive waivers eliminating the requirement to conduct pediatric *cancer studies*.²²² Children with cancer have been victims of pharmaceutical companies abusing loopholes within the law.²²³ Exemptions in PREA "have been broadly applied to cancer."²²⁴ Legislation originally introduced in 2016 and reintroduced February of 2017 has aimed to end this abuse.²²⁵ The

214. See Jerles, *supra* note 13, at 522.

215. *Id.*; see also § 402, 121 Stat. at 866.

216. Jerles, *supra* note 13, at 522; see also § 402, 121 Stat. at 868–69.

217. Jerles, *supra* note 13, at 522; see also § 402, 121 Stat. at 874–75.

218. *Childhood Cancers*, *supra* note 2.

219. See *Childhood Cancers Research*, NAT'L CANCER INST., <http://www.cancer.gov/research/areas/childhood> (last updated Sept. 1, 2017).

220. Jerles, *supra* note 13, at 528, 531–32; see also Best Pharmaceuticals for Children Act of 2007, Pub. L. No. 110-85, § 502, 121 Stat. 876, 876 (codified as amended in 21 U.S.C.); § 402, 121 Stat. at 866; Fernandez Lynch, *supra* note 7, at 94–95.

221. Adamson et al., *supra* note 7, at 737.

222. *Id.*

223. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

224. *Id.*

225. *Id.*; see also Research to Accelerate Cures and Equity for Children Act, H.R. 1231, 115th Cong. § 2 (as introduced in House, Feb. 27, 2017); Research to Accelerate

Research to Accelerate Cures and Equity for Children Act (“RACE”) was introduced to improve children’s access to new, promising drugs—thus improving current cancer treatments considerably.²²⁶ “RACE updates the 2003 PREA law,” which requires pediatric testing during development of adult drugs.²²⁷ RACE updates PREA to more adequately reflect current advances in oncology drug development by removing the exemptions, which have halted the development of new pediatric cancer drugs.²²⁸

A. *The Issues RACE Aims to Resolve*

BPCA and PREA have generated major safety and labeling data for several children’s diseases.²²⁹ Despite producing hundreds of successful cases which provide incredible data on drug use in children, “[PREA] has never been applied to a pediatric cancer drug.”²³⁰ The current PREA law was written with some significant loopholes, which are in the form of *broad exemptions* in pediatric cancer drug development, thus awarding drug manufacturers a *waiver* from completing pediatric studies.²³¹ PREA requires pharmaceutical companies to conduct pediatric testing while developing a drug for use in adults.²³² These loopholes have prevented children with cancer from accessing the newest and most promising drugs.²³³ As drug development in oncology has advanced over the past fifteen years, these issues have arose out of the language of PREA not growing simultaneous with those advances.²³⁴ Currently, instead of targeting specific types of cancers, drugs are developed by targeting genes and proteins that are shared in children and adults.²³⁵ This method is called *molecular targeting*.²³⁶

Cures and Equity for Children Act, S. 456, 115th Cong. § 2 (as introduced in Senate, Feb. 27, 2017).

226. KIDS V CANCER, *supra* note 5; *see also* H.R. 1231 § 2; S. 456 § 2.

227. McCaul et al., *supra* note 33.

228. *See id.*; KIDS V CANCER, *supra* note 5.

229. *A RACE to the Finish!*, *supra* note 25.

230. McCaul et al., *supra* note 33.

231. *Id.*

232. *A RACE to the Finish!*, *supra* note 25.

233. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

234. *See* Allen, *supra* note 26; McCaul et al., *supra* note 33.

235. Allen, *supra* note 26.

236. *Id.*

The current approach to licensing drugs is based on their pathological indication rather than their mechanism of action, even though the drug target for a common adult cancer, such as ALK in non-small-cell lung cancer, can be present and therapeutically relevant in a pathologically distinct childhood cancer, such as neuroblastoma.

Adamson et al., *supra* note 7, at 737.

PREA has not benefitted children because children's cancer initiates in different parts of the body than adult cancers.²³⁷ Due to the current PREA law, drug manufacturers receive waivers for drugs that target adult cancers because the common adult cancers these drugs are being developed for, do not occur in children.²³⁸ However, some pediatric cancers share the same molecular targets as adult cancers, despite originating in different organs.²³⁹ Due to the language of the legislation, PREA only applies when the diseases are the same in both the child and the adult, meaning the cancer has to originate in the same part of the body.²⁴⁰ This results in the first exemption that has constrained PREA's impact on children with cancer.²⁴¹ Under PREA, treatments developed for conditions in adults that do not effect children are exempt from the requirements of pediatric testing.²⁴² Thus, pediatric studies during drug development can only be required where the drug is being studied for the same disease or *indication* in both adults and children.²⁴³ Because children do not develop many of the identical adult cancers, pediatric studies are not performed.²⁴⁴

Another exemption to PREA's required pediatric testing applies when the drug "ha[s] received [an] orphan designation," given when a drug is being developed for a rare disease.²⁴⁵ A drug receives an orphan designation when it affects 200,000 people or fewer in the United States.²⁴⁶ Due to scientific advances, the "ability to define the molecular basis of an individual's cancer means that diagnoses have become increasingly subdivided, and the majority of approved cancer drugs now carry this orphan designation."²⁴⁷ Recently, with this improved ability, has come a drastic increase in the number of orphan designations.²⁴⁸ With no changes in the last

237. *KIDS V CANCER*, *supra* note 5.

238. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

239. *KIDS V CANCER*, *supra* note 5. As an example, children with neuroblastoma have been successfully treated by an ALK inhibitor that treats adults with lung cancer. *Id.*

240. *See* Allen, *supra* note 26; McCaul et al., *supra* note 33.

241. *A RACE to the Finish!*, *supra* note 25.

242. *Id.*; *see also* *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

243. *A RACE to the Finish!*, *supra* note 25.

244. *See id.*

245. McCaul et al., *supra* note 33; *see also* *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

246. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

247. *Id.*

248. *See id.*

fifteen years, the law has not been able to keep pace with medicine, thus leaving children with a lack of updated treatment options.²⁴⁹

B. *RACE to the Finish: The Impact of this Proposed Legislation*

RACE is designed to fix the problems that riddle PREA and further increase the opportunities for pediatric studies involving children with cancer.²⁵⁰ RACE gives the FDA the necessary authority to require pediatric investigation when drugs are being developed using molecular targeting and the target identified in the adult cancer is *substantively relevant* to a form of pediatric cancer.²⁵¹ PREA requirements would apply to any therapy with a molecular target that is relevant in both adult and childhood cancers; it does not matter what part of the body the cancer existed or if it is the same type of disease.²⁵² This will help provide accurate labeling on drugs for pediatric use, “allow[ing] doctors to [establish correct] dosage[s], safety, and efficacy in children.”²⁵³ As new treatments emerge and proper dosages are studied, doctors will no longer have to prescribe children *off-label* adult drugs and can eventually prescribe drugs developed specifically for use in children.²⁵⁴

Additionally, RACE will end PREA’s pediatric study exemption of orphan designated drug development.²⁵⁵ RACE requires *pediatric investigation* during development of adult orphan drugs—no matter how many people are afflicted by the disease and no matter where the cancer originates in the body.²⁵⁶ Lastly, RACE includes an incentive to companies that submit *pediatric study plans* early, which includes earlier FDA’s input on those plans.²⁵⁷ The bill even attends to the most *serious* and *life-threatening diseases* in children, as it directs the FDA to work with pharmaceutical companies to speed up development of drugs in these situations.²⁵⁸ Currently, treatment is limited for children suffering from some

249. Allen, *supra* note 26.

250. See *A RACE to the Finish!*, *supra* note 25.

251. McCaul et al., *supra* note 33.

252. See *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466. Studies have already saved lives where the links between adult and pediatric molecular targets led to treatment. McCaul et al., *supra* note 33. Some forms of pediatric neuroblastoma contain the same ALK gene that appears in adult lung cancers. *Id.* ALK inhibiting treatment that was developed for adult lung cancer has proven effective in certain neuroblastoma cases. *Id.*

253. McCaul et al., *supra* note 33.

254. *Id.*; Allen, *supra* note 26.

255. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

256. McCaul et al., *supra* note 33.

257. *KIDS V CANCER*, *supra* note 5.

258. H.R. 1231 § 2(b)(1)(i)(I)–(II); S. 456 § 2(b)(1)(I)–(II).

of the most challenging forms of cancer, but “[t]he RACE for Children Act could be the game-changer that finally offers children and their families the best standard of care possible.”²⁵⁹

V. CONCLUSION

Children’s involvement in medicine has always been a conundrum of sorts.²⁶⁰ History has revealed that children have been on a proverbial rollercoaster when it comes to their involvement in medicinal practices.²⁶¹ At first, children lacked rights and were even considered as *chattel*—belonging to their parents.²⁶² Once the public was aware of the abuse children were subjected to through clinical trials and studies, progress was slowly made.²⁶³ As time passed, in the eyes of the public and the government, children became a vulnerable class as they could not protect themselves due to their lack of rights.²⁶⁴ Due to public outcry, the government felt the need to safeguard children from the types of abuses they had endured in the past.²⁶⁵

As medicine progressed over the course of the late twentieth century, regulations were placed to further protect children from clinical trials and studies.²⁶⁶ Though the intentions were sincere, these regulations slowed down and even halted the development of new pediatric drugs and treatments.²⁶⁷ While drugs had been developed for well-known and common diseases, childhood cancer patients were often overlooked.²⁶⁸ Despite general medical advances, the regulations in place provided little reason for pharmaceutical companies to develop drugs for pediatric use, especially for childhood cancer.²⁶⁹

259. McCaul et al., *supra* note 33.

260. See Breslow, *supra* note 21, at 135–136; Ross & Walsh, *supra* note 49, at 320.

261. See Breslow, *supra* note 21, at 135–136; Ross & Walsh, *supra* note 49, at 320.

262. Breslow, *supra* note 21, at 136.

263. See Fernandez Lynch, *supra* note 7, at 98; Ross & Walsh, *supra* note 49, at 320.

264. See Fernandez Lynch, *supra* note 7, at 98; Oberman & Frader, *supra* note 40, at 301.

265. See Breslow, *supra* note 21, at 138–39; Oberman & Frader, *supra* note 40, at 301.

266. See Breslow, *supra* note 21, at 138–39; Oberman & Frader, *supra* note 40, at 301.

267. See Fernandez Lynch, *supra* note 7, at 85–86; Oberman & Frader, *supra* note 40, at 301.

268. See Lynch, *supra* note 7, at 86.

269. *Id.*

In the late 1990s, with momentum carrying into the 2000s, Congress tried to take a stand to improve the availability of drugs for children.²⁷⁰ Programs were enacted to provide incentives for pharmaceutical companies to test drugs in children to provide adequate labeling and other programs were enacted to require testing in pediatric populations to hopefully result in new treatments.²⁷¹ As with many laws, these had to be reenacted upon expiration to continue the progress but also to patch some holes within the writing of the laws.²⁷²

Despite having overall success in many pediatric fields, these laws did little to positively impact childhood cancer and the children suffering from it.²⁷³ The laws in place were focused mainly on adult drugs, with little development in drugs specifically for use in children, which incentivized companies to test on adult drugs already on the market rather than formulate drugs specifically for children.²⁷⁴ Loopholes in the most current laws providing waivers to required pediatric testing have allowed companies to avoid testing in childhood cancer all together, leaving children without treatment designed for their specific illness.²⁷⁵

A new bill has been introduced to Congress that would end the waiver exemptions.²⁷⁶ RACE updates the existing law to properly correlate with the medical progress made over the last fifteen years.²⁷⁷ “RACE . . . catches . . . the law [up] with the science”²⁷⁸ Rick Allen, who represents the Twelfth Congressional District of Georgia, has called this *commonsense legislation*, and if there was ever a time to classify it as such, the time is now.²⁷⁹ As of July 2017, the House of Representatives included RACE in a larger piece of legislation, the FDA Reauthorization Act of 2017, which unanimously passed in the House.²⁸⁰ The passage of this legislation is crucial in the fight to save children’s lives, as expressed by U.S. Senator Chris Van Hollen when he professed:

270. *Id.* at 93.

271. *See* Breslow, *supra* note 21, at 133–34.

272. *See* Jerles, *supra* note 13, at 519, 528.

273. Adamson et al., *supra* note 7, at 737.

274. Jerles, *supra* note 13, at 531–32.

275. *See* Fernandez Lynch, *supra* note 7, at 96–97; Jerles, *supra* note 13, at 521–22.

276. *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

277. Allen, *supra* note 26; *Cures for All: US Lawmakers Should Give Drug Firms the Confidence to Test Cancer Therapies in Children*, *supra* note 18, at 466.

278. *KIDS V CANCER*, *supra* note 5.

279. Allen, *supra* note 26.

280. *Id.*

No childhood should be interrupted by a struggle for survival, but cancer tragically puts far too many kids in Maryland and across the country in a battle for their lives. Researchers at institutions like the National Institutes of Health have made important progress on cancer research, and our laws need to reflect this. House passage of this legislation brings us an important step closer to updating statutes around drug development to reflect recent advancements to research, which will help save children and their families from the misery of this horrific disease.²⁸¹

The passage of RACE would provide many new treatments for pediatric cancer patients, leading to many more birthdays all while giving families hope for a successful RACE to a cure.²⁸²

281. Press Release, Michael Bennet, Senator Bennet, Rubio, Van Hollen, Gardner Applaud House Passage of RACE for Children Act (July 12, 2017) (on file with author).

282. *KIDS V CANCER*, *supra* note 5. The author would like to add that since the writing of this Comment, the RACE for Children Act has been signed into law as Title V of the FDA Reauthorization Act, amending the Pediatric Research Equity Act, otherwise known as PREA. Hopefully this leads to waiving the checkered flag, successfully completing the RACE to a cure.