

NOTE

PROVING CAUSATION IN CLINICAL RESEARCH NEGLIGENCE

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Investigators conducting clinical research create a risk of harm to their human subjects. The common law recognizes a variety of duties that these investigators owe to their subjects. When they breach these duties, such as by negligently designing the study or failing to obtain informed consent, subjects who experience a negative outcome relative to not having participated in the study should be able to maintain a cause of action for negligence against the investigators.

Yet when researchers are negligent, it will often be impossible to show whether the study caused any individual subject's injuries. The infamous SUPPORT study, in which researchers should have reasonably foreseen that they were exposing randomly selected infants to a higher risk of death, is one example. As the subsequent litigation over that study showed, traditional principles of causation operate to make it difficult or impossible for research subjects to pursue such claims against investigators. This is because the factual circumstances of most clinical research preclude individual plaintiffs from being able to show that their injuries were more-likely-than-not caused by their participation in the study.

The loss of chance doctrine developed in medical malpractice suits provides one potential solution for overcoming this causation problem. An even better solution, which provides optimal deterrence and as-good-as-possible compensation for injured subjects, would be for courts to adopt a theory of "marginal causation," which permits proof of causation by the aggregate marginal damages suffered by plaintiffs

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as a group, as an extension of the existing doctrines of loss of chance and alternative liability.

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INTRODUCTION

Human-subjects research is vital for advancing scientific and medical knowledge. In particular, the development of new drugs relies on studies carried out on human volunteers. The COVID-19 pandemic and the corresponding race to develop a vaccine have placed the risks and rewards

of medical research in the spotlight.¹ While there is much concern about the safety of potential vaccines for the public,² scant attention has been placed on the risks to participants in the preclinical trials, which include tens of thousands of volunteers.³ Indeed, three COVID-19-vaccine clinical trials were halted due to safety concerns.⁴ Although nothing suggests that these studies have deviated from appropriate ethical standards,⁵ the demand for a speedy solution and the prospect of financial reward create complicated ethical pressures.⁶ Besides these highly publicized Phase 3 trials, the National Institutes of Health (“NIH”) reports that there are currently 947 studies conducting human-subjects research on COVID-19.⁷

Beyond COVID-19, NIH reports that there are 34,907 studies involving human subjects that are recruiting, enrolling, or active in the United States.⁸ If carried out correctly, these studies, on COVID-19 or

¹ See, e.g., Carl Zimmer, Jonathan Corum & Sui-Lee Wee, Coronavirus Vaccine Tracker, N.Y. Times, <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html> [https://perma.cc/MTG4-6P9H] (last visited Oct. 20, 2020).

² Katie Thomas, Experts Tell FDA It Should Gather More Safety Data on Covid-19 Vaccines, N.Y. Times (Nov. 9, 2020), <https://www.nytimes.com/2020/10/22/health/covid-vaccine-fda-advisory-committee.html> [https://perma.cc/A8AY-SFJE].

³ William A. Haseltine, The Risks of Rushing a COVID-19 Vaccine, Sci. Am. (June 22, 2020), <https://www.scientificamerican.com/article/the-risks-of-rushing-a-covid-19-vaccine/> [https://perma.cc/QG6D-P26G].

⁴ Carl Zimmer, 3 Covid-19 Trials Have Been Paused for Safety. That’s a Good Thing., N.Y. Times (Nov. 23, 2020), <https://www.nytimes.com/2020/10/14/health/covid-clinical-trials.html> [https://perma.cc/J377-L6Z2].

⁵ Id. Monitoring and reacting appropriately to adverse events are part of routine clinical research. See FDA, Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection 3–6 (2009), <https://www.fda.gov/media/72267/download> [https://perma.cc/AE2L-ANDA].

⁶ U.S. Dep’t Health & Hum. Servs., Explaining Operational Warp Speed (2020), <https://www.nihb.org/covid-19/wp-content/uploads/2020/08/Fact-sheet-operation-warp-speed.pdf> [https://perma.cc/94NK-MVJL]; Emily A. Wang, Jonathan Zenilman & Lauren Brinkley-Rubinstein, Ethical Considerations for COVID-19 Vaccine Trials in Correctional Facilities, 324 JAMA 1031 (2020); Euzebiusz Jamrozik & Michael J. Selgelid, COVID-19 Human Challenge Studies: Ethical Issues, 20 Lancet Infectious Diseases e198, e199–e202 (2020).

⁷ ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cntry=US&Search=Apply&recrs=a&recrs=f&recrs=d&age%20_v=&gndr=&type=&rslt= [https://perma.cc/RC4E-CTK8] (last visited Oct. 1, 2021) (selecting “COVID-19” for “Condition or disease,” “United States” for “Country” and “Recruiting,” “Enrolling by invitation,” and “Active, not recruiting” from “Status”).

⁸ ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cntry=US&Search=Apply&recrs=a&recrs=f&recrs=d&age%20_v=&gndr=&type=&rslt= [https://perma.cc/XR6G-GPFA] (last

otherwise, will advance the collective knowledge of society, increase the quality of medical treatment, and save lives. But these studies also risk treating their human subjects as merely a means to a scientific end.⁹ An ethical violation of this nature is particularly insidious in the context of medical research, where subjects often place their trust in medical professionals. Yet clinical research differs from medical treatment because medical professionals conducting research are not acting for the benefit of any specific patient, but rather are attempting to generate scientific knowledge. Any benefit to a specific subject is incidental.¹⁰

The history of medical research in the United States, including the forty-year failure of the Tuskegee Syphilis Study to obtain consent from, inform, or treat nearly 400 Black men infected with syphilis¹¹ shows that investigators in this country are capable of reprehensible research.¹² Tort law ought to provide a safeguard against such ethical failures. But it fails to do so because satisfying the traditional requirements of causation is impossible for most clinical research. The loss of chance doctrine, familiar in the medical malpractice context, should be accepted as a means of satisfying causation in clinical research cases. The best way for tort law to address clinical research harms is to extend the canonical *Summers v. Tice* doctrine of alternative liability to loss of chance.¹³ This Note calls this proposed approach “marginal causation.”

In Part I, this Note discusses the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial Study (“SUPPORT study”), which is a salient instance of possible clinical research negligence. There are good reasons to believe that this study was negligent in its informed consent process and in its design. Yet institutional review boards approved the study and investigators conducted it. While negligence for the research was litigated in *Looney v. Moore*, the application of Alabama’s traditional

visited Oct. 1, 2021) (selecting “United States” for “Country” and “Recruiting,” “Enrolling by invitation,” and “Active, not recruiting” from “Status”).

⁹ Immanuel Kant, *Groundwork for the Metaphysics of Morals* 46–47 (Allen W. Wood ed. & trans., Yale Univ. Press 2002) (1785) (“The practical imperative will thus be the following: *Act so that you use humanity, as much in your own person as in the person of every other, always at the same time as end and never merely as means.*”).

¹⁰ See *infra* Section II.A.

¹¹ CDC, The Tuskegee Timeline, <https://www.cdc.gov/tuskegee/timeline.htm> [https://perm a.cc/422Y-SUUX] (last visited Nov. 19, 2019).

¹² Frederick Adams, Foreword to Vivien Spitz, *Doctors from Hell: The Horrific Account of Nazi Experiments on Humans*, at xv, xv–xxvii (2005).

¹³ 33 Cal. 2d 80 (1948).

causation doctrine by the trial and appellate courts prevented the plaintiff-subjects from even reaching a jury.¹⁴

As Part II describes, there is a sufficient foundation existing in the common law for the courts of most jurisdictions to find that legal duties exist between investigators and subjects in clinical research and that their breach is legally cognizable. Nonetheless, the particular factual circumstances of clinical research preclude subjects from proving causation under traditional negligence doctrine. Investigators' conduct itself shields them from liability when they negligently conduct their research on human subjects.

Part III explores a potential solution to the failure of traditional doctrine to address clinical research harms in the doctrine of loss of chance, which courts have developed in the face of similar challenges for plaintiffs in medical malpractice actions. It also discusses how the law of mass exposure torts provides a parallel for clinical research negligence. This Part concludes by suggesting that the factual circumstances of clinical research are best met through an extension of the canonical *Summers v. Tice* doctrine of alternative liability from defendants to plaintiffs. The theory, which this Note terms "marginal causation," proposes that when a class of vulnerable plaintiffs can show that it collectively suffered a marginal aggregate injury because of a defendant's conduct, common law courts should permit individual injured plaintiffs to recover for the likelihood that their injuries were actually caused by the defendant's conduct.

I. CASE STUDY

The SUPPORT study and the litigation that followed provide a stark example of how traditional negligence principles fail to address harms that arise from negligent clinical research. Section A describes the study and demonstrates how enrollment in the study may have led to blindness or death for some infants. It also shows how investigators were likely negligent with respect to informed consent and design. Section B describes the case of *Looney v. Moore*, which was filed on behalf of study participants against study investigators. It describes how the court applied traditional causation doctrine and precluded plaintiffs from reaching a jury despite the negligence and nearly certain harms.

¹⁴ 18 F. Supp. 3d 1338 (N.D. Ala. 2014), aff'd, 886 F.3d 1058 (11th Cir. 2018).

A. The SUPPORT Study

The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial Study (“SUPPORT study”) was a clinical study carried out on a group of 1,316 premature infants.¹⁵ Premature infants require oxygen support, but high levels of oxygen saturation create a risk of “retinopathy of prematurity” (“ROP”), which can cause blindness.¹⁶ The study consent forms indicated that the standard of care was to keep oxygen levels between 85% and 95%.¹⁷ The stated purpose of the study was to assess whether the lower range of oxygen levels, 85% to 89%, would be associated with a lower risk of ROP without compromising safety.¹⁸ The study noted that prior studies had raised concerns about the safety levels of lower oxygen levels.¹⁹

The study randomly assigned enrolled infants into a low oxygen-saturation range between 85% and 89% (“low-oxygen group”) or a higher oxygen-saturation range between 91% and 95% (“high-oxygen group”).²⁰ The study was blinded by using modified oxygen meters that indicated that the infant’s oxygen level was either 3% higher or lower than actually measured so that the reported range was always 88% to 92%.²¹ The oximeters were modified to provide this false information to ensure that the infants received the amount of oxygen specified for their group, that the clinical team did not change its behavior based on the infant’s true status, and to ensure that the clinical team did not intentionally avoid the high or low ranges of the oxygen levels.²²

The study found that 19.9% of the infants in the low-oxygen group died before discharge, as compared to 16.2% of the infants in the high-oxygen

¹⁵ SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Target Ranges of Oxygen Saturation in Extreme Preterm Infants, 362 New Eng. J. Med. 1959, 1964 (2010) [hereinafter SUPPORT Study].

¹⁶ Id. at 1960.

¹⁷ See, e.g., Duke Univ. Health Sys., Minor’s Consent to Participate in a Research Study, The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial, 2 (June 27, 2007) (on file with the author) [hereinafter Minor’s Consent to Participate].

¹⁸ SUPPORT Study, supra note 15, at 1960.

¹⁹ Id.

²⁰ Id. at 1961.

²¹ Id.

²² Robert J. Morse & Robin Fretwell Wilson, Realizing Informed Consent in Times of Controversy: Lessons from the SUPPORT Study, 44 J.L. Med. & Ethics 402, 408 (2016).

group.²³ The study also found that severe ROP occurred in 8.6% of the low-oxygen group and 17.9% of the high-oxygen group.²⁴ The investigators forthrightly stated that, for subjects in the low-oxygen group, “our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented.”²⁵ And they also noted that only follow-up data collection would show “the effects of lower target ranges of oxygen saturation on functional visual and neurodevelopmental outcomes.”²⁶ Thus, whether an infant was randomly allocated to one group or the other measurably affected both their chance of survival and their likelihood of suffering serious visual impairment.

The study generated a significant ethical controversy shortly after publication of its results.²⁷ In 2013, the Office for Human Research Protections (“OHRP”), which oversees all federally-funded human-subjects research, sent a letter to the University of Alabama at Birmingham (“UAB”) stating that the UAB consent forms were defective.²⁸ The letter recognized that the study range described the standard of care, but noted that physicians, in treating their own patients, might have chosen to avoid the extreme ends of the range.²⁹ Other consent forms for the study disclosed that the “aim in many [Neonatal Intensive Care Units (“NICUs”)] is to keep oxygen saturations between 88 and 92%.”³⁰ In addition, the director of the OHRP told the press “that the consent form was written in a ‘slanted way’” because the form suggested that the infants might benefit from participation in the study without

²³ SUPPORT Study, *supra* note 15, at 1965. The adjusted relative risk for being in the high oxygen group was 1.27 with a 95% confidence interval from 1.01 to 1.60. *Id.*

²⁴ *Id.* This produced an adjusted relative risk ratio of 0.52 with a 95% confidence interval of 0.37 to 0.73. *Id.*

²⁵ *Id.* at 1967.

²⁶ *Id.* at 1966–67.

²⁷ Sue Coons, *The SUPPORT Trial: Risk and Consent Questions Divide the Clinical Research Community*, 14 *Rsch. Prac.* 112, 112–13 (2013).

²⁸ See Benjamin S. Wilfond et al., *The OHRP and SUPPORT*, 368 *New Eng. J. Med.* e36(1) (2013); Ruth Macklin et al., *The OHRP and SUPPORT – Another View*, 369 *New Eng. J. Med.* e3(1)(2013); Letter from Lisa R. Buchanan, Compliance Oversight Coordinator, Div. of Compliance Oversight, Off. for Human Rsch. Prots., to Richard B. Marchase, V.P. for Rsch. & Econ. Dev., Univ. of Ala. at Birmingham (June 4, 2013) [*hereinafter Letter from Lisa R. Buchanan*].

²⁹ See Macklin et al., *supra* note 28.

³⁰ Letter from Lisa R. Buchanan, *supra* note 28 (quoting Minor’s Consent to Participate, *supra* note 17, at 2).

adequately disclosing that they could end up worse off.³¹ In the benefits section of the consent form, UAB implied that a possible benefit of being in the low-oxygen group was a lower chance of developing ROP. Despite the pre-existing safety concerns regarding the low-oxygen range,³² the risks section of the same consent form failed to disclose the possibility that being in the lower-oxygen group could raise the risk of death or neurodevelopmental problems.³³ The errors made in the study consent forms are particularly stark in comparison to the consent forms provided to participants in the New Zealand counterpart to the study.³⁴ Those consent forms acknowledged the reasonably foreseeable risks specific to the low-oxygen and high-oxygen groups, respectively.³⁵ The defects in the SUPPORT study informed consent process could be the basis of a breach of the investigators' duty to obtain informed consent.³⁶

Although the OHRP stated it "does not and has never questioned whether the design of the SUPPORT study was ethical,"³⁷ there is significant cause for concern because of the lack of a control group. The study tested the hypothesis that the lower oxygen saturation would reduce the composite risk of ROP and death.³⁸ As stated previously, many NICUs aimed to keep oxygen saturation between 88% and 92%.³⁹ That is the group against which the composite risk of ROP and mortality should have been assessed. Because the SUPPORT study only compared the low-oxygen group to the high-oxygen group, which differs from the typical treatment, it remains unclear whether or not either the low-oxygen group or the high-oxygen counterpart presents a preferred profile of risks compared to the standard treatment regime. As a result, the study's design precluded it from achieving its primary purpose. And because it could not achieve that purpose, the study could not generate useful scientific

³¹ See Coons, *supra* note 27, at 114.

³² See Letter from Lisa R. Buchanan, *supra* note 28, at 2 (referencing Minor's Consent to Participate, *supra* note 17); see also SUPPORT Study, *supra* note 15, at 1960 (discussing previous studies and stating that "the safety of low target levels of oxygen saturation remains a concern").

³³ Univ. of Ala. at Birmingham, Informed Consent, The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Study) (Multicenter Network of Neonatal ICU's) 4–5 (May 5, 2008) (on file with author).

³⁴ Morse & Wilson, *supra* note 22, at 411.

³⁵ Id.

³⁶ See *infra* Section II.C.

³⁷ See Letter from Lisa R. Buchanan, *supra* note 28, at 1.

³⁸ See SUPPORT Study, *supra* note 15, at 1960.

³⁹ See *supra* note 30 and accompanying text.

knowledge. Conducting a negligently designed study exposes human subjects to risks without justification and could be a breach of investigators' duty to take reasonable care in designing the study.⁴⁰

Other bioethicists have argued that the lower oxygen group was not the standard of care anywhere.⁴¹ While clinical research must sometimes deviate from the standard of care, and a worse result for a treatment group does not necessarily or even probably indicate negligence, knowingly providing strictly inferior care would be unethical.⁴² If investigators nevertheless did so, that could breach the investigators' duty to not cause subjects to bear unjustifiable risks.⁴³

B. Looney v. Moore

In 2013, the parents of several infants enrolled in the SUPPORT study brought a class action lawsuit in federal court against the University of Alabama Review Board, the study investigators, and Masimo Corporation, which manufactured the modified oximeters used in the study.⁴⁴ The plaintiffs were the parents of one child who was placed in the high-oxygen group and developed retinopathy of prematurity and two other children who were placed in the low-oxygen group and developed neurodevelopmental issues.⁴⁵ They alleged negligence in the study's design, negligence per se for failure to comply with the Common Rule,⁴⁶ lack of informed consent, breach of fiduciary duty, and products liability.⁴⁷ All of the defendants filed motions for summary judgment for

⁴⁰ See *infra* Section II.C.

⁴¹ See George J. Annas & Catherine L. Annas, "Unusual Care": Groupthink and Willful Blindness in the SUPPORT Study, 20 *Am. J. Bioethics* 44, 45 (2020) ("The therapeutic illusion led them to inaccurately describe both arms of SUPPORT as 'standard of care' treatment.").

⁴² See *id.*; Benjamin Freedman, Equipoise and the Ethics of Clinical Research, 317 *New Eng. J. Med.* 141 (1987).

⁴³ See *infra* Section II.C.

⁴⁴ Fifth Amended Class Action Complaint and Jury Trial Demand at 5, *Looney v. Moore*, 18 F. Supp. 3d 1338 (N.D. Ala. 2014) (No. 2:13-cv-00733-UNAS), 2014 WL 1631450. The modified oximeters were used to "blind" the medical professionals who carried out the study by showing oxygen levels that differed from the actual measurements. SUPPORT Study, *supra* note 15, at 1961.

⁴⁵ *Looney v. Moore*, No. 2:13-cv-00733, 2015 WL 4773747, at *3 (N.D. Ala. Aug. 13, 2015), aff'd, 886 F.3d 1058 (11th Cir. 2018).

⁴⁶ The Common Rule is the set of regulations specifying the requirements for research on human subjects to qualify for federal funding. See *infra* notes 85–89 and accompanying text.

⁴⁷ *Id.*; see also Fifth Amended Class Action Complaint, *supra* note 44.

failure “to present sufficient evidence to create a genuine issue of material fact as to whether the SUPPORT study *caused* the Plaintiffs’ injury.”⁴⁸

The plaintiffs’ expert had testified that participation in the SUPPORT study “increased the risk [that the Plaintiffs] would suffer from the physical and other problems of the type or even more severe than they now experience.”⁴⁹ In doing so, the expert was invoking the loss of chance doctrine, which permits the causation element of negligence to be satisfied by an increased risk of death or injury, rather than by the traditional more-likely-than-not causation standard.⁵⁰ I discuss this doctrine in more detail in Section III.A. After reviewing the pertinent testimony of both parties’ experts, the court held that the plaintiffs “fail[ed] to create a genuine issue of material fact as to whether their participation in the SUPPORT study probably caused their injuries.”⁵¹

On appeal, the Eleventh Circuit reiterated that Alabama law required that medical malpractice plaintiffs must adduce some evidence that the alleged negligence *probably* caused the injury.⁵² The court noted that the plaintiffs’ expert “never testified that the SUPPORT study caused Plaintiffs’ medical ailments, or even that the SUPPORT study *probably* caused the ailments; he opined only that the study ‘significantly increased the risk’ that they would suffer from such ailments.”⁵³ Their expert’s testimony that the study “significantly increased the risk” the plaintiffs would suffer from study-related ailments was not “evidence that the SUPPORT study ‘probably’ caused their injuries.”⁵⁴ The court, therefore, found that the plaintiffs’ claims were not viable under Alabama law and affirmed the district court’s grant of summary judgment.⁵⁵

C. The Failure of Tort Law

The SUPPORT study and *Looney v. Moore* illustrate how the tort system fails to address injuries arising from clinical research. Like much clinical research, the SUPPORT study was conducted on individuals who were already in a precarious position. The trial court noted that the

⁴⁸ *Looney*, 2015 WL 4773747, at *4.

⁴⁹ *Id.* at *7.

⁵⁰ See *infra* Section III.A.

⁵¹ *Looney*, 2015 WL 4773747, at *9.

⁵² *Looney v. Moore*, 886 F.3d 1058, 1062 (11th Cir. 2018).

⁵³ *Id.* at 1063.

⁵⁴ *Id.* at 1063–64.

⁵⁵ *Id.* at 1064.

plaintiffs' extremely premature births had "already put them at a very high risk of developing ROP or neurological issues."⁵⁶ But those vulnerabilities are exactly why the investigators identified the infants for their study and then exposed them to additional risk. Furthermore, the differences in the outcomes between the two groups in the SUPPORT study suggest that some subjects in each group suffered negative outcomes that they would not have suffered but for their participation in the study.⁵⁷ And the risks that manifested for the low-oxygen group were reasonably foreseeable: the investigators explicitly said that "the safety of low target levels of oxygen saturation remains a concern."⁵⁸ Yet, as the litigation in *Looney* shows, no individual SUPPORT subject that experienced a negative outcome can prove causation under traditional principles. The basic problem is that no plaintiff can prove cause-in-fact through but-for causation because the plaintiffs' pre-existing vulnerabilities dominate the causal chain.⁵⁹ In its remaining Parts, this Note discusses the legal theories supporting a common law cause of action for clinical research negligence and extends several theories of causation to support their viability.

II. NEGLIGENCE ACTIONS FOR CLINICAL RESEARCH

This Part discusses the general theory supporting negligence causes of action. Section A distinguishes clinical research from medical treatment and describes the relevant features of clinical research. Section B describes the development of an international consensus on the ethical duties of investigators conducting research on human subjects. Section C describes the duties that investigators owe to subjects. It also discusses

⁵⁶ *Looney*, 2015 WL 4773747, at *7.

⁵⁷ See supra Section I.A. Despite the study results, some defend the study and even suggest that participants in the study were better off than non-participants. See John D. Lantos, Learning the Right Lessons from the SUPPORT Study Controversy, 99 Archives of Disease in Childhood Fetal Education F4 (2014); Waldemar A. Carlo, Edward F. Bell & Michele C. Walsh, Oxygen-Saturation Targets in Extreme Preterm Infants, 368 New Eng. J. Med. 1949 (2013). This Note's position is that, when there is a plausible claim that clinical research has led to harm, this question is one of fact to be settled through litigation.

⁵⁸ SUPPORT Study, supra note 15, at 1960; see also Ruth Macklin & Charles Natanson, Misrepresenting "Usual Care" in Research: An Ethical and Scientific Error, 20 Am. J. Bioethics 31, 35 (2020) ("[T]he lower oxygen saturation range was not standard clinical practice.").

⁵⁹ See *Paroline v. United States*, 572 U.S. 434, 449–56 (2014) (discussing the difficulty of applying traditional but-for causation in criminal restitution when an individual defendant's role in inflicting a large harm is small).

cases that have recognized legal duties between an investigator and research subjects. Section D shows how the factual circumstances of clinical research make it nearly impossible for injured subjects to prove causation under traditional doctrine.

A. Clinical Research Versus Medical Treatment

The term “clinical research” includes research on treatment, prevention, diagnostic screening, quality of life, genetic studies, and epidemiological studies.⁶⁰ The precise purpose of clinical research varies by study, but in a general sense, all well-designed clinical research evaluates a specific medical question to generate knowledge for the benefit of future patients.⁶¹ For this Note, clinical research means studies on human subjects that evaluate specific interventions on health outcomes through a randomized, controlled protocol.⁶² Treatment research, like the SUPPORT study, is one common form of clinical research that compares different treatments.⁶³ Another common type is clinical trials, which evaluate new medical interventions on human subjects.⁶⁴

Clinical research and medical treatment bear certain similarities. Medical professionals, including physicians and nurses, often conduct both clinical research and medical treatment.⁶⁵ Both treatment and research involve the use of interventions including medical techniques, devices, products, and medications.⁶⁶ Some subjects seek to participate in clinical trials because standard therapy has failed.⁶⁷ The similarities between the two have given rise to the “therapeutic misconception,” which refers to the mistaken idea that clinical research is intended to

⁶⁰ FDA, What are the Different Types of Clinical Research?, (Jan. 4, 2018), <https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-type-s-clinical-research> [https://perma.cc/4WHE-RCST].

⁶¹ Id. See Ezekiel J. Emanuel, David Wendler & Cristine Grady, What Makes Clinical Research Ethical?, 283 JAMA 2701, 2703 (2000).

⁶² FDA, Clinical Research Versus Medical Treatment (Mar. 22, 2018), <https://www.fda.gov/patients/clinical-trials-what-patients-need-know/clinical-research-versus-medical-treatment> [https://perma.cc/D3CE-2MXY].

⁶³ FDA, supra note 60.

⁶⁴ Id.

⁶⁵ See Izet Masic, Aijla Hodzic & Smaila Mulic, Ethics in Medical Research and Publication, 5 Int’l J. Preventative Med. 1073, 1075 (2014).

⁶⁶ See generally FDA, supra note 60 (describing different types of clinical research).

⁶⁷ FDA, supra note 62.

benefit the individual subjects.⁶⁸ Medical treatment relies on interventions that the medical community accepts as effective and safe, while clinical research often involves interventions whose purported benefits have not been proven.⁶⁹

There are, however, fundamental differences between medical treatment and clinical research. The purpose of medical treatment is to address the needs of individual patients for their benefit, while the purpose of clinical research is to answer specific scientific or medical questions for the benefit of future patients.⁷⁰ Medical treatment requires real-time decision making, whereas clinical research decision making depends on the research protocol.⁷¹ While patient assessment for medical treatment happens as needed, clinical research involves periodic and systematic assessment of subject data.⁷² Finally, patients generally have access to information about medical-treatment interventions through product labeling, but information about clinical research interventions is often considered confidential intellectual property.⁷³

B. Ethical Duties of Clinical Investigators

It is widely acknowledged that investigators owe certain duties to human subjects. The beginning of rigorous ethical analysis of these duties is generally traced to the trials of Nazi physicians for the horrific and cruel experiments they conducted on human subjects.⁷⁴ The verdict of those trials produced the Nuremberg Code, which consisted of ten propositions regarding ethical human experimentation.⁷⁵ Seventeen years later, the

⁶⁸ Morse & Wilson, *supra* note 22, at 407 (citing Paul S. Appelbaum, Loren H. Roth, Charles W. Lidz, Paul Benson & William Winslade, *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 Hastings Ctr. Rep. 20 (1987)).

⁶⁹ FDA, *supra* note 62.

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² *Id.*

⁷³ *Id.*

⁷⁴ Emanuel et al., *supra* note 61, at 2701–02; see Spitz, *supra* note 12, at 3–5.

⁷⁵ Nuernberg Military Tribunals, 2 Trials of War Criminals Before the Nuernberg Military Tribunals Under Control Council Law No. 10, at 181–82 (1949). The requirements relevant here included, *inter alia*, that human subjects voluntarily consent, that the experiment should produce knowledge benefiting society, that the degree of risk must not exceed the humanitarian importance of the knowledge generated, that protections should be provided for subjects against the possibility of injury, disability or death, that the experiment should be conducted only with the highest degree of skill and care, and that the scientist in charge must be prepared to terminate the experiment if it is likely to result in injury, disability, or death. *Id.*

World Medical Association published the Declaration of Helsinki,⁷⁶ which was “developed to remedy perceived lacunae in the Nuremberg Code.”⁷⁷

Investigators in the United States have committed their own grave wrongs in research on human subjects.⁷⁸ In 1966, Dr. Beecher published “Ethics and Clinical Research,” calling attention to twenty-two instances of unethical research after World War II, including a case where effective treatment for typhoid was withheld and another where live cancer cells were inserted into human subjects.⁷⁹ Over the next few years, revelations about the profoundly unethical studies at Tuskegee and Willowbrook came to light.⁸⁰ The Tuskegee Syphilis Study followed four hundred Black men who had syphilis for forty years without obtaining their informed consent, informing them of their illness, or providing them with readily available treatment.⁸¹ In the Willowbrook Study, investigators systematically infected developmentally disabled children and adults with hepatitis.⁸²

The Belmont Report, published in response to these abuses,⁸³ developed three basic ethical principles: (1) respect for persons; (2) beneficence; and (3) justice, with applications to informed consent, assessment of risk and benefits, and selection of subjects.⁸⁴ The recommendations of the Belmont Report were eventually included in federal regulations as the Common Rule.⁸⁵ This regulation applies to “all

⁷⁶ World Med. Ass’n, Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (1964). The Declaration has since been amended in 1975, 1983, 1989, 1996, 2000, 2008, and 2013.

⁷⁷ Emanuel et al., *supra* note 61, at 2702.

⁷⁸ See generally David S. Jones, Christine Grady & Susan E. Lederer, “Ethics and Clinical Research” — The 50th Anniversary of Beecher’s Bombshell, 374 New Eng. J. Med. 2393 (2016) (describing contemporary and late twentieth-century medical research controversies).

⁷⁹ Henry K. Beecher, Ethics and Clinical Research, 274 New Eng. J. Med. 1354, 1356, 1358 (1966).

⁸⁰ CDC, *supra* note 11; David J. Rothman, Were Tuskegee & Willowbrook ‘Studies in Nature’?, 12 Hastings Ctr. Rep., Apr. 1982, at 5, 5–6.

⁸¹ CDC, *supra* note 11. Syphilis is treated with penicillin. *Id.*

⁸² Rothman, *supra* note 80, at 6. The Willowbrook study was also cited by Dr. Beecher. Beecher, *supra* note 79, at 1358.

⁸³ Emanuel et al., *supra* note 61, at 2702.

⁸⁴ Nat'l Comm'n for the Prot. of Hum. Subjects of Biomedical and Behav. Rsch., The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research 4, 10 (1978).

⁸⁵ 45 C.F.R. § 46.101 (2018); see also U.S. Dep’t of Health & Hum. Servs., Federal Policy for the Protection of Human Subjects (‘Common Rule’), <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html> [https://perma.cc/XR55-HZET] (last

research involving human subjects conducted, supported, or otherwise subject to regulation” by the federal government.⁸⁶ The Common Rule requires Institutional Review Board (“IRB”) approval of human-subjects research⁸⁷ and mandates certain requirements for and documentation of informed consent.⁸⁸ Research institutions typically agree to apply the requirement of the Common Rule to all qualifying research, regardless of funding.⁸⁹ Do these ethical duties, or correlates to them, sound in tort? As the next section discusses, courts have recognized some of them.

C. Legal Duties Owed to Research Subjects

Investigators must owe some duties to subjects. Even setting aside special ethical considerations of human-subjects research, investigators owe subjects the ordinary duty to act reasonably.⁹⁰ The early literature on the matter largely concluded that the investigator-subject relationship was a fiduciary one modeled on the physician-patient relationship.⁹¹ This initially seems natural, given that physicians conduct much clinical research.⁹² Should courts generally adopt this view, then the principles governing physician-patient relationships and medical malpractice could be imported into the investigator-subject context. To date, however, no

visited Nov. 19, 2019) (explaining that current federal human subjects regulations were heavily influenced by the Belmont Report).

⁸⁶ 45 C.F.R. § 46.101 (2018).

⁸⁷ 45 C.F.R. § 46.111 (2018).

⁸⁸ 45 C.F.R. §§ 46.116–46.117 (2018).

⁸⁹ Stanley G. Korenman, *Common Rule, Teaching the Responsible Conduct of Research in Humans* (2006), <https://ori.hhs.gov/education/products/ucla/chapter2/page04b.htm> [<https://perma.cc/SF6F-NAZY>].

⁹⁰ See *Ande v. Rock*, 647 N.W.2d 265, 272 (Wis. Ct. App. 2002) (rejecting a medical malpractice claim against researchers on the basis that there was no physician-patient relationship, but only duties from ordinary negligence principles).

⁹¹ Angela R. Holder, *Do Researchers and Subjects Have a Fiduciary Relationship?*, 4 IRB: Ethics & Hum. Rsch 6 (1982) (stating that Jay Katz, an eminent medical ethicist, concluded that the researcher-subject relationship was fiduciary and describing the implications for researcher disclosure to subjects); see also Nat'l Comm'n for the Prot. of Hum. Subjects of Biomedical and Behav. Rsch., *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* app. vol. I at 3-7, 3-82 (1979) (“[I]nformed consent is a type of contract in which one of the contractors (the investigator)--as in all fiduciary relationships--is held accountable for higher standards of responsible conduct than are most individuals in creating commercial contracts.”).

⁹² See Carl H. Coleman, *Duties to Subjects in Clinical Research*, 58 Vand. L. Rev. 387, 392 (2005) (arguing for courts to adopt a fiduciary model).

American court has recognized a fiduciary duty between investigators and subjects, and they are right not to do so.

In his later work, medical ethicist Jay Katz argued that, for investigators, “loyalty to the research protocol will take precedence over faithfulness to the therapeutic mission.”⁹³ That loyalty would be inconsistent with a fiduciary’s duty of loyalty.⁹⁴ Recognizing this inherent conflict, Haavi Morreim has argued that investigators must place their loyalty first to the protocol as a matter of research ethics.⁹⁵

It is straightforward to see why the duties of a physician and an investigator are incompatible. For physicians, loyalty to the patients means acting in their best interests by providing individualized therapeutic treatment that is responsive to their personal medical situations and developments.⁹⁶ Investigators, however, must preserve the scientific validity of the study,⁹⁷ which entails a study with “a clear scientific objective” and “designed using accepted principles, methods, and reliable practices.”⁹⁸ Two practices that are crucial for ensuring reliability are randomization and blinding. Randomization means that the investigator cannot choose which treatment arm of a study would be in an individual subject’s best interest,⁹⁹ and blinding means that the investigator does not know which study treatment the subject is

⁹³ Jay Katz, Human Experimentation and Human Rights, 38 St. Louis U. L.J. 7, 29 (1993).

⁹⁴ Holder, *supra* note 91, at 6.

⁹⁵ E. Haavi Morreim, Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve, 4 *Hous. J. Health L. & Pol'y* 1, 44–45 (2003).

⁹⁶ See Robert J. Levine, Ethics and Regulation of Clinical Research 10 (2d ed. 1988) (“[T]he individualized dosage adjustments and changes in therapeutic modalities are less likely to occur in the context of a clinical trial than they are in the practice of medicine. This deprivation of the experimentation ordinarily done to enhance the well-being of a patient is one of the burdens imposed on the patient-subject [in] a clinical trial.”); Lynn A. Jansen, Taking Respect Seriously: Clinical Research and the Demands of Informed Consent, 43 *J. Med. & Phil.* 342, 349 (2018).

⁹⁷ Emanuel et al., *supra* note 61, at 2704.

⁹⁸ Id.

⁹⁹ Evan G. DeRenzo & Joel Moss, Writing Clinical Research Protocols: Ethical Considerations 186–87 (2006). Randomization is the “process of selecting groups for comparison of the efficacy of one intervention over another.” *Id.* at 186. It safeguards scientific validity by enhancing the likelihood that the groups receiving the study interventions are comparable at the baseline. *Id.* That contributes to the validity of causal inferences by reducing the probability that observed differences in outcomes are attributable to the treatment and not to unobserved differences between the groups. See Franklin G. Miller, The Ethics of Placebo-Controlled Trials, in *The Oxford Textbook of Clinical Research Ethics* 261, 262 (Ezekiel J. Emanuel et al. eds., 2008).

receiving.¹⁰⁰ And if those restrictions were not enough to make it impossible for investigators to provide individualized treatment, they also must preserve the scientific validity of the protocol by refusing to deviate from it, even when doing so might be in an individual subject's best interest.¹⁰¹ Those duties are squarely incompatible with the physician's duty of loyalty.

As expected, then, courts have not been willing to recognize a fiduciary duty between investigators and subjects unless that duty is first established in a pre-existing relationship.¹⁰² Instead, state courts have looked to other sources of duties. In *Whitlock v. Duke University*, an early case on the issue, a federal trial court sitting in diversity and applying North Carolina law examined a set of claims arising from an alleged injury suffered by a participant in an experiment that simulated a dive to a depth of 2,250 feet.¹⁰³ The court distinguished between therapeutic experimentation, which involved healthcare, and non-therapeutic experimentation, which did not.¹⁰⁴ Because this was non-therapeutic, the court held that North Carolina's informed consent statute did not apply to the case.¹⁰⁵ But, after concluding that the Nuremberg Code and the Declaration of Helsinki always required subjective consent, the court held that the duty to obtain informed consent was governed by 45 C.F.R. § 46 and that "the degree of required disclosure of risks is *higher* in the nontherapeutic context."¹⁰⁶

Similarly, in *Grimes v. Kennedy Krieger Institute, Inc.*, the Maryland Supreme Court reviewed a case arising from a non-therapeutic research

¹⁰⁰ Double-blinding is a procedure to ensure that "neither the subject nor the investigator knows to which study arm the subject has been assigned." DeRenzo & Moss, *supra* note 99, at 186. Blinding reduces bias by reducing the likelihood that subjects and research personnel behave differently because of their knowledge of the intervention they are receiving. Paul J. Karanicolas, Forough Farrokhyar & Mohit Bhandari, *Blinding: Who, What, When, Why, How?*, 53 Can. J. Surgery 345, 345–46 (2010).

¹⁰¹ E. Haavi Morreim, *The Clinical Investigator as Fiduciary: Discarding a Misguided Idea*, 33 J.L. Med. & Ethics 586, 590 (2005) ("If [the researcher] deviates from the protocol every time it might suit the volunteer, he will destroy its scientific validity.").

¹⁰² *Moore v. Regents of Univ. of Cal.*, 793 P.2d 479, 483 (Cal. 1990) (finding a fiduciary obligation of disclosure for a physician who used his patient's cells for medical research and economic gain).

¹⁰³ 637 F. Supp. 1463, 1466 (M.D.N.C. 1986), aff'd per curiam, 829 F.2d 1340 (4th Cir. 1987).

¹⁰⁴ *Id.* at 1470.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at 1470–71 (emphasis added).

study carried out at Johns Hopkins University.¹⁰⁷ The investigators had subsidized partial lead abatement in certain residences and encouraged landlords to rent them to families with young children.¹⁰⁸ Their study examined the efficacy of different lead-abatement procedures by measuring the lead dust in the premises and the lead contamination in the children's blood.¹⁰⁹ Under these facts, the court held that informed consent agreements and the federal regulations for federally funded research on human subjects embodied in 45 C.F.R. § 46 can give rise to a common law "special relationship."¹¹⁰

Notably, the court then proceeded to analyze the "ethical appropriateness" of the research with reference to the Declaration of Helsinki and the Code of Nuremberg.¹¹¹ It stated that "[s]cience cannot be permitted to be the sole judge of the appropriateness of such research methods on human subjects, especially in respect to children."¹¹² Finding that persuasive authority supported a finding that parents could not consent for their children to non-therapeutic research,¹¹³ the court concluded that "no degree of parental consent, and no degree of furnished information to the parents could make the experiment at issue here, ethically or legally permissible. It was wrong in the first instance."¹¹⁴ These cases show that courts can and should recognize duties that protect the interests of subjects of clinical research.

These possible common law duties arise from our ethical expectations of investigators. For example, the requirement to obtain informed consent—long recognized for medical treatment—is a natural fit.¹¹⁵ Another example is the requirement that there be a favorable risk-benefit ratio.¹¹⁶ Breaching this duty means that investigators have exposed their subjects to an unjustifiable risk. The same is true for studies that lack scientific validity or social or scientific value.¹¹⁷ These duties should

¹⁰⁷ 782 A.2d 807, 812 (Md. 2001).

¹⁰⁸ Id.

¹⁰⁹ Id. at 812–13.

¹¹⁰ Id. at 843–50.

¹¹¹ Id. at 849–52.

¹¹² Id. at 855.

¹¹³ See *T.D. v. N.Y. State Off. of Mental Health*, 650 N.Y.S.2d 173, 191–92 (App. Div. 1995).

¹¹⁴ *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 857–58 (Md. 2001).

¹¹⁵ See *Mohr v. Williams*, 104 N.W. 12, 14–15 (Minn. 1905), overruled in part by *Genzel v. Halvorson*, 80 N.W.2d 854 (Minn. 1957).

¹¹⁶ See *Emanuel et al.*, *supra* note 61, at 2703.

¹¹⁷ Id.

support tort suits for subjects that wind up injured because of their participation. And the same is doubly true for studies that fail to use fair subject selection or to treat enrolled subjects with respect.¹¹⁸ Breaches of those ethical requirements raise grave concerns about whether the study is just. Like in other areas of life, the law should provide plaintiffs with a remedy when investigators breach these important duties.

D. The Problem of Causation

The elements of negligence are duty, breach, causation, and damages. As discussed above, courts have accepted duties arising from federal regulations and special relationships.¹¹⁹ Besides breaches of informed consent, negligence actions could lie for failing to minimize risks to subjects, failing to ensure that risks are reasonable, and for inequitable selection of subjects.¹²⁰ The failure to comply with the additional protections that apply to research on pregnant women, human fetuses, neonates, prisoners, and children could also plausibly serve as the basis for negligence duties.¹²¹ Others could arise from the study design that compromises scientific validity and consequently the study's justification for exposing human subjects to risks.¹²² There are many plausible and viable ways for subjects of negligent clinical research to establish duty and breach, and a variety of commentators have articulated plausible standards of conduct.¹²³ Breach of duty is not a hurdle for plaintiffs. Rather, it is proving causation in clinical research negligence that is tremendously more difficult than usual.¹²⁴

In any well-designed study, traditional causation doctrine will present plaintiffs with a nearly impossible hurdle. Causation requires the plaintiff to prove cause-in-fact and proximate cause by a preponderance of the evidence. Much clinical research, however, involves studying treatment options in “clinical equipoise,” which means that there “is genuine

¹¹⁸ *Id.*

¹¹⁹ See supra notes 91, 106, 110 and accompanying text.

¹²⁰ 45 C.F.R. § 46.111 (2018).

¹²¹ 45 C.F.R. §§ 46.203–46.205, 46.305–46.306, 46.404–46.408 (2018).

¹²² Morreim, *supra* note 95, at 38–39 (“To expose human beings to excessive risk, or even to moderate risk or mere inconvenience if the protocol is scientifically feeble, would arguably be negligence.”).

¹²³ See *id.* at 41–45; Valerie G. Koch, *A Private Right of Action for Informed Consent*, 45 Seton Hall L. Rev. 173, 207 (2015); Coleman, *supra* note 92, at 444–45.

¹²⁴ See Lori A. Alvino, *Who’s Watching the Watchdogs? Responding to the Erosion of Research Ethics by Enforcing Promises*, 103 Colum. L. Rev. 893, 912 (2003).

uncertainty within the expert medical community . . . about the preferred treatment.”¹²⁵ The idea behind this type of research is to compare two treatment options and observe marginal differences in various outcomes such as efficacy, mortality, and morbidity. The studied outcomes emerge in the form of statistically significant differences between individuals randomly assigned to treatment and control groups. Statistical significance captures the likelihood that the observed effect is a result of a genuine difference between the sample groups and not merely the result of chance.¹²⁶ It does not require that an effect have a large magnitude.¹²⁷

A well-designed and sufficiently powered study can detect small differences with a high degree of statistical significance.¹²⁸ A typical research study between two treatment options might detect a marginal ten percent increase in the relative risk of five-year mortality for one treatment for an illness versus another. A study producing such a result might involve 2,000 subjects evenly divided into a treatment group and a control group. In the treatment group, which received the novel treatment, suppose 220 subjects died, while in the control group, which received the best available therapy, 200 subjects died.

Of course, not every study in which one group experiences a worse outcome will be negligent—that would make clinical research impossible. But suppose the researchers breached some duty to the subjects: they did not obtain informed consent, they knew the novel treatment was inferior, or they failed to design the study so that it could generate generalizable knowledge. Even with breach clearly established, it would be impossible for any subject to show that assignment to the novel treatment group more-likely-than-not caused their death. This is

¹²⁵ See generally Benjamin Freedman, Equipoise and the Ethics of Clinical Research, 317 *New Eng. J. Med.* 141 (1987) (proposing clinical equipoise replace “equipoise” as an ethical requirement for clinical research). Equipoise was the idea that the clinical investigator herself was in a “a state of genuine uncertainty” about the “comparative merits of treatments.” *Id.*

¹²⁶ David M. Lane et al., Introduction to Statistics, Online Statistics Education: A Multimedia Course of Study 375–76, http://onlinestatbook.com/Online_Statistics_Education.pdf [<https://perma.cc/M79J-BDBS>] (last visited Nov. 23, 2019).

¹²⁷ *Id.*

¹²⁸ *Id.* at 378. Statistical power refers to the probability of “correctly rejecting a false null hypothesis,” which means the likelihood of detecting an effect if it actually exists. *Id.* Statistical power increases with sample size, or the number of subjects in the treatment groups. See Frederick J. Dorey, In Brief: Statistics in Brief: Statistical Power: What Is It and When Should It Be Used?, 469 *Clinical Orthopaedics and Related Rsch.* 619, 620 (2011). An insufficiently powered clinical study would expose subjects to risk without being able to generate scientifically valuable knowledge.

because these research subjects already faced a serious risk of death due to their pre-existing medical condition—the condition that led them to qualify for the study in the first place.¹²⁹ But we know that if the novel treatment group had received the best available therapy, twenty fewer individuals would have been expected to die. The death of these twenty additional individuals is the result of these researchers’ conduct, but because it cannot be traced to any specific subject, none of the subjects could prove that participation in the study caused their injuries. Like in many medical malpractice cases, the actions of the negligent party make “it impossible for the plaintiff to prove that he or she would have achieved that better outcome.”¹³⁰ As Part III proposes, the marginal effects revealed by the study should themselves become the basis for a new form of causation applicable to these circumstances: a theory that this Note calls marginal causation.

III. ESTABLISHING CAUSATION

This Part develops a solution to the inability of plaintiffs to establish causation in clinical research tort actions. Section A discusses the development of the loss of chance doctrine as a solution to similar difficulties facing plaintiffs in proving causation in medical malpractice claims. Section B describes the similarities and differences between the general factual circumstances of medical malpractice, mass exposure torts, and clinical research. Section C proposes the doctrine of marginal causation as an extension of the doctrine of alternative liability, as established in the canonical case of *Summers v. Tice*, to plaintiffs in appropriate circumstances. Section D demonstrates how damages would be calculated under the various causation theories developed in this Part. Finally, Section E concludes by applying these theories to the SUPPORT study.

A. Loss of Chance as a Solution to Causation in Medical Malpractice

The idea that traditional causation can preclude intuitively meritorious claims is not new. The first case usually cited as examining this issue is

¹²⁹ SUPPORT Study, *supra* note 15; see also Kathy L. Hudson, Alan E. Guttmacher & Francis S. Collins, In Support of SUPPORT — A View from the NIH, 368 New Eng. J. Med. 2349, 2351 (2013) (explaining that the infants enrolled in SUPPORT “fac[ed] substantial risks because of prematurity”).

¹³⁰ Smith v. Providence Health & Servs.—Or., 393 P.3d 1106, 1115 (Or. 2017).

Hicks v. United States, a Fourth Circuit decision applying Virginia law.¹³¹ That court stated in dicta that any substantial lost possibility of survival would permit a negligent physician to be held liable.¹³² *Hicks* started a general recognition of the doctrine in various jurisdictions.¹³³ As the doctrine evolved over the next half-century, three main forms emerged.¹³⁴ The first formulation applies the doctrine by relaxing the causation standard for a negligence claim.¹³⁵ The second treats the loss of chance as a compensable injury itself.¹³⁶ The third is a hybrid approach that relaxes the traditional causation standard while also limiting damages to the chance lost.¹³⁷

1. Loss of Chance as a Relaxed Causation Requirement

An example of the first form is shown in *Roberson v. Counselman*, in which the Kansas Supreme Court considered an appeal from summary judgment for the defendant where the plaintiff's evidence suggested that her husband had lost a forty percent chance of survival.¹³⁸ The court specifically assessed the evidence in terms of causation and noted that Section 323 of the Second Restatement of Torts relaxed the standard for causation.¹³⁹ Section 323 provides that

One who undertakes, gratuitously or for consideration, to render services to another which he should recognize as necessary for the protection of the other's person or things, is subject to liability to the other for physical harm resulting from his failure to exercise reasonable care to perform his undertaking, if

(a) his failure to exercise such care increases the risk of such harm . . .¹⁴⁰

The court held that there was sufficient evidence to submit the question of whether the increased risk from the defendant's negligence was a

¹³¹ See, e.g., 1 Steven E. Pegalis, American Law of Medical Malpractice § 5:3, at 388–89 (Thomson/West 3d ed. 2005).

¹³² *Hicks v. United States*, 368 F.2d 626, 632 (4th Cir. 1966).

¹³³ *Kramer v. Lewisville Mem'l Hosp.*, 858 S.W.2d 397, 400–02 (Tex. 1993).

¹³⁴ *Id.*

¹³⁵ *Id.* at 401.

¹³⁶ *Id.* at 402.

¹³⁷ *Id.*

¹³⁸ 686 P.2d 149, 150–51 (Kan. 1984).

¹³⁹ *Id.* at 157 (citing *Jones v. Montefiore Hosp.*, 431 A.2d 920, 923–24 (Pa. 1981)).

¹⁴⁰ Restatement (Second) of Torts § 323 (Am. L. Inst. 1965).

substantial factor in causing the death of the plaintiff's husband.¹⁴¹ The court, therefore, modified the meaning of "substantial factor" to encompass causes where less than a more-likely-than-not chance of survival is lost.¹⁴²

Other courts have adopted the reduced causation formulation without expressly invoking Section 323.¹⁴³ For example, the Supreme Court of Virginia held in *Brown v. Koulizakis* that "in a death case, if a defendant physician, by action or inaction, has destroyed any substantial possibility of the patient's survival, such conduct becomes a proximate cause of the patient's death."¹⁴⁴ The evidence in *Brown*, however, suggested a ninety-five to ninety-eight percent chance of survival if treatment had been carried out.¹⁴⁵ This holding was affirmed in *Grieff v. Ryan*, where the same court found there was sufficient evidence to submit to a jury on the basis that a physician's failure to detect lung cancer "drastically reduced" the ultimate chance of survival for the patient.¹⁴⁶ According to the expert in that case, a timely operation "would have [had] a high likelihood" of saving the patient.¹⁴⁷

The New York appellate court made a clearer statement of the doctrine, without reasoning through Section 323, in *Kallenberg v. Beth Israel Hospital*.¹⁴⁸ In that case, the court upheld a jury verdict for the plaintiff against a proximate cause challenge based on expert testimony that a patient would have had a twenty to forty percent chance of recovery in the absence of the negligence of medical personnel.¹⁴⁹ This case also

¹⁴¹ *Roberson*, 686 P.2d at 160.

¹⁴² Accord *Hamil v. Bashline*, 392 A.2d 1280, 1287–88 (Pa. 1978) ("Section 323(a) . . . permits the issue to go to the jury upon a less than normal threshold of proof."); *Thompson v. Sun City Cnty. Hosp., Inc.*, 688 P.2d 605, 616 (Ariz. 1984).

¹⁴³ Because it could be contested that clinical research investigators "render services to another which [they] should recognize as necessary for the protection of the other's person," it is important to see that this formulation of loss of chance is not entirely dependent on the application of Restatement (Second) of Torts § 323. While it is clear that physicians who commit medical malpractice fall within this provision, it is less clear for investigators. Nonetheless, investigators do render certain services which are necessary for the protection of the subjects. They are responsible, for example, for designing the study ethically and obtaining informed consent, which could be construed as "services," provided gratuitously, but also necessary for the protection of the subjects.

¹⁴⁴ 331 S.E.2d 440, 446 (Va. 1985).

¹⁴⁵ *Id.*

¹⁴⁶ 443 S.E.2d 149, 151–52 (Va. 1994).

¹⁴⁷ *Id.* at 152.

¹⁴⁸ 357 N.Y.S.2d 508 (App. Div. 1974).

¹⁴⁹ *Id.* at 510–11.

highlights one of the most problematic aspects of the relaxed causation approach: it still permits recovery for the entire value of the wrongful death.¹⁵⁰ In a subsequent case, however, a New York court stated that *Kallenberg* required a finding that “there was a substantial possibility that the decedent would have recovered but for the malpractice.”¹⁵¹

2. *Loss of Chance as a Separate Compensable Injury*

The second theory, that loss of chance should be a separate compensable injury, was first put forward by Professor King.¹⁵² He argued that “a chance of avoiding some adverse result or of achieving some favorable result is a compensable interest in its own right.”¹⁵³ He distinguished this theory from treating loss of chance as a valuation issue or a causation issue.¹⁵⁴ If loss of chance itself is a compensable injury, traditional causation principles could still apply because the plaintiff would still have to prove by a preponderance of the evidence that the defendant’s negligent conduct diminished the chance of a better outcome by at least the amount that the plaintiff claimed.¹⁵⁵ An important corollary of this view is that damages should be adjusted to match the loss of chance amount.¹⁵⁶ Thus, on the facts of *Roberson*, for example, if the jury believed the plaintiff’s evidence and concluded that the plaintiff’s husband had indeed lost a forty percent chance of survival, the award should be forty percent of the award had it been a typical wrongful death suit.

The Supreme Court of Washington gave this formulation of the loss of chance doctrine its initial recognition in *Herskovits v. Group Health Cooperative of Puget Sound*.¹⁵⁷ That court held that evidence of a reduction in the chance for survival from thirty-nine percent to twenty-

¹⁵⁰ *Id.* at 509, 511 (upholding the jury verdict intact with its substantial damages award); see also *Herskovits v. Grp. Health Coop. of Puget Sound*, 664 P.2d 474, 484 (Wash. 1983) (Pearson, J., concurring) (describing *Kallenberg* as taking an “extreme approach” by upholding the full jury verdict).

¹⁵¹ *Kimball v. Scors*, 399 N.Y.S.2d 350, 351 (App. Div. 1984); see also *Mortensen v. Mem'l Hosp.*, 483 N.Y.S.2d 264, 268–69 (App. Div. 1984) (explaining why *Kallenberg* should not be read to hold that any reduced chance of survival is grounds for a claim).

¹⁵² Joseph H. King, Jr., *Causation, Valuation, and Chance in Personal Injury Torts Involving Preexisting Conditions and Future Consequences*, 90 Yale L.J. 1353, 1381 (1981).

¹⁵³ *Id.* at 1354.

¹⁵⁴ *Id.* at 1363.

¹⁵⁵ *Id.* at 1394–95.

¹⁵⁶ *Id.* at 1381–87 (discussing methods of valuing loss of chance).

¹⁵⁷ 664 P.2d 474 (Wash. 1983).

five percent was sufficient to permit a jury to consider proximate cause.¹⁵⁸ In doing so, the court noted that “[t]o decide otherwise would be a blanket release from liability for doctors and hospitals any time there was less than a 50 percent chance of survival, regardless of how flagrant the negligence.”¹⁵⁹ The majority then limited damages to those “caused directly by premature death, such as lost earnings and additional medical expenses, etc.”¹⁶⁰ The concurring opinion, which four of the six-judge majority joined, would have recognized the loss of chance itself as an actionable injury with damages limited according to Professor King’s theory.¹⁶¹ Other courts have explicitly adopted this formulation as a separate cause of action in medical malpractice cases.¹⁶² Several state courts of last resort have recognized this form of the doctrine in the last ten or so years, suggesting that this is the prevailing contemporary trend.¹⁶³

3. Loss of Chance as Relaxed Causation and Lost Chance Damages

An example of the third formulation, which reduces the causation threshold in medical malpractice but also limits damages, can be found in the Oklahoma Supreme Court’s opinion in *McKellips v. Saint Francis Hospital, Inc.*¹⁶⁴ That case involved a patient who died from a heart attack after he had been allegedly negligently released from supervision by a doctor.¹⁶⁵ An expert witness testified that, while he could not answer whether continued observation would have changed the outcome, it

¹⁵⁸ Id. at 476–77.

¹⁵⁹ Id. at 477.

¹⁶⁰ Id. at 479.

¹⁶¹ Id. at 487.

¹⁶² See *Wollen v. DePaul Health Ctr.*, 828 S.W.2d 681, 685 (Mo. 1992) (“[R]ather than adopting a theory of proportional causation, this Court chooses to recognize a cause of action for lost chance of recovery in medical malpractice cases.”); *Perez v. Las Vegas Med. Ctr.*, 805 P.2d 589, 592 (Nev. 1991) (“By defining the injury as the loss of chance of survival, the traditional rule of preponderance is fully satisfied.”).

¹⁶³ See *Smith v. Providence Health & Servs.—Or.*, 393 P.3d 1106, 1121 (Or. 2017) (“[A] loss of a substantial chance of a better medical outcome can be a cognizable injury in a common-law claim of medical malpractice.”); *Dickhoff ex rel. Dickhoff v. Green*, 836 N.W.2d 321, 334 (Minn. 2013) (adopting the position that treats “the reduction of a patient’s chance of recovery or survival as a distinct injury”); *Matsuyama v. Birnbaum*, 890 N.E.2d 819, 838 (Mass. 2008) (recognizing loss of chance as “a separate, compensable item of damages in an action for medical malpractice”).

¹⁶⁴ 741 P.2d 467 (Okla. 1987).

¹⁶⁵ Id. at 470.

would have “significantly improved” his chances of survival.¹⁶⁶ The court held that “in a limited type of medical malpractice case where the duty breached was one imposed to prevent the type of harm which a patient ultimately sustains,” the plaintiff’s evidentiary burden was lowered.¹⁶⁷ “In effect,” the court stated, “the lowered standard merely reallocates the power to decide the causation issue, giving the jury a greater role in the decision making process.”¹⁶⁸ The court then went on to hold that the damages award must be reduced so that “recovery is permitted only for the percent of chance lost times the total amount of damages which are ordinarily allowed.”¹⁶⁹

Since its inception in *Hicks*, loss of chance has developed into an important doctrine in state common law. A recent collection of loss of chance cases suggested that over twenty states have recognized the doctrine, while ten states have rejected it.¹⁷⁰ Oregon and Minnesota, which were listed as rejecting the doctrine, have since accepted it.¹⁷¹ The states that have accepted it, however, have been scrupulous in limiting it to medical malpractice cases.¹⁷² But the logic behind the doctrine readily extends to clinical research negligence.

B. Medical Malpractice and Mass Exposure as Models

The nature of clinical research negligence is comparable to two other classic tort contexts: medical malpractice and mass exposure. The clinical research setting is an ideal synthesis of these two types of tort cases. It presents some of the challenges typical of both types of suits: namely, it is difficult for plaintiffs to establish causation, but it also presents the opportunity for the law to enact a more accurate and precise form of justice.

Clinical research is like medical treatment in that it involves the application of medical interventions to or monitoring of human beings.¹⁷³ Because of the personal and invasive nature of the central conduct,

¹⁶⁶ *Id.*

¹⁶⁷ *Id.* at 474.

¹⁶⁸ *Id.* at 475.

¹⁶⁹ *Id.* at 477.

¹⁷⁰ *Matsuyama v. Birnbaum*, 890 N.E.2d 819, 828 n.23 (Mass. 2008).

¹⁷¹ *Smith v. Providence Health & Servs.—Or.*, 393 P.3d 1106, 1121 (Or. 2017); *Dickhoff ex rel. Dickhoff v. Green*, 836 N.W.2d 321, 334 (Minn. 2013).

¹⁷² See, e.g., *Smith*, 393 P.3d at 1115 (“When accepted, the loss-of-chance theory of injury in tort cases has been largely limited to the medical malpractice arena.”).

¹⁷³ FDA, *supra* note 60.

patients and subjects must give informed consent to both physicians and investigators, respectively.¹⁷⁴ Especially for so-called “therapeutic research,” clinical research, like medical malpractice, often involves conducting procedures on subjects with pre-existing illnesses and comorbidities.¹⁷⁵ Finally, clinical research resembles medical malpractice in that the injuries arising from it involve deterioration in health or death. In medical malpractice, the principal reason for adopting loss of chance is that it is “the alleged medical malpractice itself that makes it impossible for the plaintiff to prove that he or she would have achieved that better outcome.”¹⁷⁶ As discussed above, the clinical research study design and methods make it impossible for the plaintiff to prove that he or she could have achieved a better outcome if he or she had not participated.¹⁷⁷ Thus, when a study proceeds after an investigator has breached a duty owed to a subject, it is the study, negligently conducted, that precludes a plaintiff from establishing causation. For those courts that have accepted the doctrine for medical malpractice cases, there are sufficient similarities between medical malpractice and clinical research—including its central rationale—to justify extending the doctrine to clinical research.

Clinical research has other attributes that make it even more hospitable to the loss of chance doctrine than traditional medical malpractice. This is because clinical research cases resemble mass exposure torts. Clinical research and mass exposure cases both involve “numerous persons suffering the same or similar injuries as a result of a single pattern of misconduct on the part of a defendant.”¹⁷⁸ Crucial attributes shared between these two sorts of cases are centralized sources of injury, statistical predictability, large scales, and a high degree of relative

¹⁷⁴ *Canterbury v. Spence*, 464 F.2d 772, 793 (D.C. Cir. 1972) (for patients); *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 849 (Md. 2001) (for subjects).

¹⁷⁵ Alvino, *supra* note 124, at 912; see also Kristen R. Spencer & Janice M. Mehnert, Importance of Including Patients with Comorbidities in Clinical Trials, 17 *Lancet Oncology* 17 (2016) (discussing inclusion of patients with co-morbidity generally); Jose M. Valderas, Barbara Starfield, Bonnie Sibbald, Chris Salisbury & Martin Roland, Defining Comorbidity: Implications for Understanding Health and Health Services, 7 *Annals Fam. Med.* 357, 358 (2009) (defining comorbidity and explaining categorization).

¹⁷⁶ *Smith*, 393 P.3d at 1115.

¹⁷⁷ See *supra* Part II.

¹⁷⁸ David Rosenberg, The Causal Connection in Mass Exposure Cases: A ‘Public Law’ Vision of the Tort System, 97 *Harv. L. Rev.* 849, 853 (1984) (quoting *In re N. Dist. of Cal. “Dalkon Shield” IUD Prod. Liab. Lit.*, 526 F. Supp. 887, 892 (N.D. Cal. 1981), vacated, 693 F.2d 847 (9th Cir. 1982)).

uniformity of disease risks.¹⁷⁹ These attributes suggest that they both “may be amenable to aggregative rather than traditional case-by-case procedures.”¹⁸⁰

In cases dealing with mass exposure, courts have expected experts to rely on epidemiological studies to show causation. For example, in *In re Ephedra Products Liability Litigation*, the defendants argued that “the only scientifically valid way to prove general causation is by controlled epidemiological studies with statistically significant results showing that ephedra (or ephedrine) materially increases the risk of the listed injuries.”¹⁸¹ In accepting the defendant’s view of science, the court held that plaintiff’s experts in a products liability case could not “testify with any degree of medical or scientific ‘certainty’” that the product at issue, ephedra, caused the alleged injuries of strokes, heart attacks, and heatstroke.¹⁸² The court, however, did permit these experts to testify “that ephedra may be a contributing cause of cardiac injury and stroke in some people,” provided that they qualify it with testimony that “there is not enough data to prove it definitively and that controlled studies, if and when they are done, may disprove it.”¹⁸³

While that court was applying Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,¹⁸⁴ its reasoning shows the strength of a study in generating evidence of medical certainty across large groups of individuals. It stands for the proposition that appropriately relevant studies bolster the ability of an expert to testify with a reasonable degree of medical certainty about the harms caused by exposure.¹⁸⁵ When a plaintiff alleges harms arising from clinical research, such a study exists as the very basis for the lawsuit. Because the study generates data across many people, the loss of chance or increased risk of harm for each subject is quantifiable to a degree of certainty that is generally impossible with an individual patient in a medical malpractice suit.

¹⁷⁹ See *id.* at 855.

¹⁸⁰ *Id.*

¹⁸¹ 393 F. Supp. 2d 181, 186 (S.D.N.Y. 2005).

¹⁸² *Id.* at 187.

¹⁸³ *Id.*

¹⁸⁴ *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), is the leading case interpreting Fed. R. Evid. 702, which controls the admissibility of expert testimony. See, e.g., *Ephedra Products*, 393 F. Supp. 2d at 187. *Daubert* requires a multifactor, flexible inquiry into whether the reasoning or methodology of the underlying testimony is scientifically valid. *Daubert*, 509 U.S. at 593–95.

¹⁸⁵ See *McClellan v. I-Flow Corp.*, 710 F. Supp. 2d 1092, 1101–02 (D. Or. 2010).

In clinical research, studies are generally designed and thoroughly controlled with specific interventions planned in advance and executed according to a protocol. A limited set of individuals constitute the subjects of any particular experiment, adherence to a specified protocol generates uniformity across the subjects allocated to one treatment or another, and randomization procedures strengthen methods of statistical prediction. As a result, there are likely to be even more statistically predictable outcomes and an even higher degree of uniformity of disease risks than in even the most favorable mass exposure case. Thus, clinical research functions as an ideal hybrid of medical malpractice, which generates the legal basis for applying loss of chance, and mass exposure, which provides the factual predicate and ethical imperative to extend the doctrine.

C. Reasons Courts Have Rejected Loss of Chance Do Not Apply to Clinical Research

State courts have rejected the loss of chance doctrine for a variety of reasons. This Section describes the four most common objections: (1) that it fails to meet a requirement that medical experts base their testimony on reasonable medical probability or certainty; (2) that the plaintiff has failed to establish causation by a preponderance of the evidence or that the defendant's conduct probably caused the injury in question; (3) that it would invite the jury to indulge in speculation and conjecture; and (4) that a less strict view of proof of causation would be unfair to the medical profession.¹⁸⁶ While these criticisms may have some merit, as they pertain to loss of chance in suits with individual plaintiffs, the unique circumstances of clinical research make them inapposite.

1. The Requirement of Reasonable Medical Probability or Certainty

Many state courts impose a standard of reasonable medical probability or reasonable medical certainty in medical malpractice cases.¹⁸⁷ In some jurisdictions, this standard attaches to causation; in others, to the plaintiff's burden of proof generally.¹⁸⁸ This standard typically operates to exclude medical testimony when experts will only testify to

¹⁸⁶ John D. Hodson, Annotation, Medical Malpractice: "Loss of Chance" Causality, 54 A.L.R.4th 10, 18 (1987).

¹⁸⁷ See Robin Kundis Craig, When *Daubert* Gets *Erie*: Medical Certainty and Medical Expert Testimony in Federal Court, 77 Denv. U. L. Rev. 69, 76 (1999).

¹⁸⁸ *Id.* at 73–74.

possibilities, which raises obvious issues for cases claiming the loss of a less-than-even chance of recovery. Definitions of reasonable medical certainty, however, are not common in the case law. One court has defined reasonable medical certainty as reflecting “an objectively well-founded conviction that the likelihood of one cause is greater than the other.”¹⁸⁹ In the negative, another court has held that a medical expert who testified that it was “feasible” that a plaintiff’s injuries were causally related to a motor vehicle injury was unable to show that his opinion was based on a reasonable medical probability.¹⁹⁰

At least two courts have rejected the loss of chance doctrine because the medical expert testimony regarding the lost chance failed to meet the standard of reasonable medical certainty.¹⁹¹ In *Odum v. Cejas*, the Missouri Court of Appeals held that an expert who testified that malpractice “significantly increased the chances” of an injury and that that injury “would have been far less likely” had proper procedures been followed had offered only “hedged, equivocal or uncertain” opinions about causation that failed as a matter of law to establish a jury question on causation.¹⁹² “[A]s a matter of medical certainty,” the court stated, “the witness simply offered uncertain opinions.”¹⁹³ And, although Illinois has adopted what appears to be a very weak form of the doctrine,¹⁹⁴ Illinois courts have continued to have concerns about whether expert witnesses can offer an opinion on the matter with reasonable certainty. For example,

¹⁸⁹ District of Columbia v. Watkins, 684 A.2d 395, 402 (D.C. 1996) (quoting Clifford v. United States, 532 A.2d 628, 640 n.10 (D.C. 1987)).

¹⁹⁰ Moses v. Drake, 109 A.3d 562, 564, 568 (Del. 2015).

¹⁹¹ See Soper v. Bopp, 990 S.W.2d 147, 150–53 (Mo. Ct. App. 1999) (stating there was “no medical evidence” that treatment would have helped the patient when the expert witness testified that a category of patients could have benefited, but could not say whether the plaintiff would have fallen into that category); see also Wingo v. Rockford Mem’l Hosp., 686 N.E.2d 722, 733–34 (Ill. App. Ct. 1997) (ruling that an expert’s opinion about causation was established with reasonable medical certainty despite the other party’s claim that that the patient’s condition had unknown causes in thirty-five percent of cases).

¹⁹² 510 S.W.2d 218, 222–25 (Mo. Ct. App. 1974).

¹⁹³ Id. at 224.

¹⁹⁴ See Holton v. Mem’l Hosp., 679 N.E.2d 1202, 1207–13 (Ill. 1997) (“We reaffirm the *Borowski* holding. The traditional statement of proximate cause requires plaintiff to prove that defendant’s negligence “more probably than not” caused plaintiff’s injury. . . . We note that the *Borowski* court’s formulation of proximate cause in the context of medical malpractice litigation is the same standard of proximate cause that is used in other types of negligence actions. . . . We hold that the loss of chance concept, when properly analyzed, does not relax or lower plaintiff’s burden of proving causation. Rather, the concept comports with the *Borowski* standard.”).

one court, applying the Illinois version of loss of chance, rejected the testimony of a medical expert as insufficient to establish proximate cause when he opined that a plaintiff might have had a twenty percent chance of saving an eye if he had been examined but failed to provide testimony about how it could have been treated.¹⁹⁵

Whether the plaintiff can proffer an expert able to testify with “reasonable medical certainty” is unlikely to be an issue for cases involving clinical research. The entire aim of a well-designed study is to generate causal inferences about the different study treatments to a reliable degree of scientific certainty.¹⁹⁶ Indeed, scientific validity depends in part on ensuring that studies have “sufficient power to definitely test the objective,” which means reducing the likelihood of a false negative.¹⁹⁷ When an injury occurs in clinical research, statistical tests on the study data can provide a very strong evidentiary basis for factual conclusions about its magnitude and the likelihood that it can be attributed to participation in the study.¹⁹⁸ An expert in statistics could perform these tests to form an “objective well-founded conviction” as the basis of their testimony.¹⁹⁹ When a study uses proper control groups, this evidence provides very strong proof of the causal connection between being in a treatment group and being in a control group.²⁰⁰ Even where proper control groups are not used, comparison between treatment groups can provide evidence about harms that easily meets the threshold for reasonable medical probability or certainty as it is typically applied in

¹⁹⁵ Reed v. Jackson Park Hosp. Found., 758 N.E.2d 868, 877–78 (Ill. App. Ct. 2001).

¹⁹⁶ Emanuel et al., *supra* note 61, at 2703.

¹⁹⁷ Id. at 2704. Formally, statistical power is the likelihood that, “[i]f the alternative hypothesis is actually true,” the study results will “will correctly reject the null hypothesis.” Frederick J. Dorey, In Brief: Statistics in Brief: Statistical Power: What Is It and When Should It Be Used?, 469 Clinical Orthopaedics and Related Rsch. 619, 619 (2011). Statistical power increases with sample size or the number of subjects in the treatment groups. Id. at 620.

¹⁹⁸ In fact, it is likely that the study data will show that the study caused some injuries at a much greater likelihood than a mere preponderance. The conventional statistical standard for rejecting the null hypothesis is a p-value of 0.05, which corresponds to a five percent likelihood that the null hypothesis is true and the observed results occurred by chance. See David M. Lane et al., *supra* note 126, at 371–78. Notably, that conventional rule for statistical significance would exclude as inconclusive a fifty-one percent to ninety-five percent chance that the null hypothesis is false even though the same chance would satisfy the law’s preponderance of the evidence standard.

¹⁹⁹ District of Columbia v. Watkins, 684 A.2d 395, 402 (D.C. 1996) (quoting Clifford v. United States, 532 A.2d 628, 640 n.10 (D.C. 1987)).

²⁰⁰ Guosheng Yin, *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods* 2 (2012).

medical malpractice cases.²⁰¹ Like in the mass exposure cases, the objection that experts in loss of chance cases cannot testify to a reasonable degree of medical probability or certainty loses its force when the expert is opining on clinical research harms.

2. Failure to Satisfy a Preponderance of the Evidence Standard

Some courts have refused to adopt loss of chance because of a concern that the doctrine involves relaxing the traditional standard of proof—preponderance of the evidence. In *Crosby v. United States*, the court examined loss of chance in a medical malpractice claim under the Alaska wrongful death statute.²⁰² Among other reasons, the court rejected loss of chance because applying it meant relaxing proof of causation to less than the preponderance standard required by the statute.²⁰³

The first way to address this objection is to follow Professor King's suggestion of treating the lost chance as a compensable injury itself.²⁰⁴ For clinical research injuries, however, there is a second way to address this objection. Unless a study is particularly egregious, no individual subject-plaintiff will be able to prove by a preponderance of the evidence that participation in the study caused their injuries. The core concern justifying the rejection of a relaxed standard of causation is the worry that it will lead to an unjust result, requiring defendants whose negligence ultimately did not cause any harm to compensate plaintiffs.²⁰⁵ In essence, relaxing causation tilts the scales against physicians by increasing the likelihood of a “false positive,” where a physician is held liable for harm that she did not cause.

Courts should recognize a distinction between proving that the study caused injuries and proving the identity of the harmed party. In medical malpractice cases with a single patient, relaxing the causation standard might create an intolerable risk that a party who did no harm will be made

²⁰¹ See id. at 10.

²⁰² 48 F. Supp. 2d 924, 930–31 (D. Alaska 1999); see also *Helms v. United States*, No. 3:11-cv-00186, 2014 WL 2561995, at *5 (D. Alaska June 6, 2014) (applying *Crosby*). Wrongful death statutes can pose an additional barrier to clinical research negligence actions when the plaintiff dies. See *United States v. Cumberbatch*, 647 A.2d 1098, 1102–04 (Del. 1994). Because this issue is more general than causation for clinical research injuries, exploring this issue must be left for another day.

²⁰³ *Crosby*, 48 F. Supp. 2d at 931.

²⁰⁴ King, *supra* note 152, at 1354.

²⁰⁵ *Crosby*, 48 F. Supp. 2d at 931 (“Plaintiffs could recover even when it was not more likely than not that any alleged malpractice caused injury.”).

to pay compensation for a negative outcome.²⁰⁶ In clinical research, on the other hand, the study data will show a higher rate of negative outcomes for certain study groups in comparison to the others. While it may not be possible to identify the specific subjects harmed by the study from the other members of the group with higher negative outcomes, this study result would imply that at least some of the negative outcomes were caused by the study.²⁰⁷ The fact that the defendants caused at least some injuries to some subjects is therefore provable by a preponderance of the evidence.

Finally, it is worth noting that this objection rests on a conflation of the traditional causation standard—more likely than not—and the traditional burden of proof—a preponderance of the evidence. It is the case that if the traditional more-likely-than-not standard is retained, a plaintiff who marshals nearly perfect evidence of a twenty percent lost chance will still have necessarily failed to meet that causation standard by a preponderance of the evidence. But under an explicitly relaxed causation standard, such as a “substantial possibility” of avoiding the injury or recovering, the plaintiff can still be required to bear the evidentiary burden of proving the loss of such substantial possibility by a preponderance of the evidence.²⁰⁸

3. Inviting Speculation and Conjecture by the Jury

Another objection arises from the concern that the loss of chance doctrine invites speculation and conjecture from the jury. In one instance, the Supreme Court of Mississippi held that instructions to a jury to consider whether there was a “good chance” of “greater recovery” of a living plaintiff’s use of his thumb were unacceptable because that language “invited impermissible speculation and conjecture.”²⁰⁹ Instead, the court held that the jury instruction should have required consideration of a “substantial probability” because Mississippi law does not permit the

²⁰⁶ Of course, the status quo is the arbitrary result in which loss of a fifty-one percent likelihood of a better outcome is fully compensable, necessarily implying that courts will tolerate a forty-nine percent chance that a defendant must compensate a plaintiff that in fact suffered no harm from the negligence. See King, *supra* note 152, at 1376.

²⁰⁷ Lane et al., *supra* note 198, at 371.

²⁰⁸ See Mortensen v. Mem’l Hosp., 483 N.Y.S.2d 264, 270–71 (App. Div. 1984) (holding that a plaintiff bears the burden of proving a substantial possibility in avoiding the injury by a preponderance of the evidence).

²⁰⁹ Clayton v. Thompson, 475 So. 2d 439, 445 (Miss. 1985).

recovery of damages for the loss of chance.²¹⁰ Similarly, the Supreme Court of Connecticut rejected a plaintiff's medical expert's testimony that it was "in the realm of possibility" that the negligent failure to operate on a patient with cancer would have prolonged her life.²¹¹ Because the expert declined to state that the patient's life being prolonged was "reasonably probable," the court found that the opinion of the jury on the matter would be "mere speculation and conjecture."²¹²

The heart of the objection regarding speculation and conjecture in medical malpractice cases stems from the complexity and difficulty of assessing the hypothetical prognosis for a patient who had received proper rather than negligent medical treatment.²¹³ This issue arises particularly in medical malpractice cases because medical malpractice is fundamentally a suit for failure to prevent the worsening of an injury, rather than a suit about the creation of the injury in the first place.²¹⁴ When clinical research is done on healthy subjects, this objection no longer applies because the bad outcomes constituting the injury would be caused by the study.²¹⁵ Of course, much clinical research is done on subjects with pre-existing illnesses or conditions, and that situation does resemble traditional medical malpractice. In clinical research cases with a proper control group, however, the factfinder will have very strong evidence of the prognosis of the harmed subjects had they not received the study intervention.²¹⁶ As a result, the factfinder may rely on the study data in

²¹⁰ *Id.*

²¹¹ *Grody v. Tulin*, 365 A.2d 1076, 1079–80 (Conn. 1976).

²¹² *Id.*

²¹³ See *id.* at 1080 ("Here, the jury would have been called upon to speculate, not as to the cause of the cancer . . . but as to whether an earlier diagnosis and treatment of the cancer might have prolonged [the plaintiff's] life.").

²¹⁴ *Clayton*, 475 So. 2d at 445 ("This Court recognizes that the plaintiff is rarely able to prove to an absolute certainty what would have happened if early treatment, referral or surgery had happened. . . . Having in mind this reality, our approach to the requirement of causation in medical malpractice cases necessarily differs from that employed in most other tort contexts.").

²¹⁵ See Patient Recruitment: Healthy Volunteers, Nat'l Insts. of Health Clinical Ctr., <https://clinicalcenter.nih.gov/recruit/volunteers.html> [<https://perma.cc/26F8-268Z>] (last visited Nov. 23, 2019) (recruiting healthy volunteers to test new drugs, devices, and interventions).

²¹⁶ See Yin, *supra* note 200 ("A *controlled* clinical trial may include an active control (the standard treatment) or a placebo (an inert that mimics the look and the route of administration of the real treatment) for direct comparison so that the difference in the clinical outcome attributable to the experimental therapy can be evaluated objectively.").

formulating its conclusions and will not need to engage in speculation and conjecture about what might have happened to harmed subjects.

4. Unfairness to the Medical Profession

Other courts have worried that the loss of chance doctrine would be unjust because of the burdens it could impose on the medical profession.²¹⁷ In *Gooding v. University Hospital Building*, the court stated that

Relaxing the causation requirement might correct a perceived unfairness to some plaintiffs who could prove the possibility that the medical malpractice caused an injury but could not prove the probability of causation, but at the same time could create an injustice. . . . No other professional malpractice defendant carries this burden of liability without the requirement that plaintiffs prove the alleged negligence probably rather than possibly caused the injury.²¹⁸

While a similar concern might exist in the clinical research context, it is significantly mitigated by two considerations. First, investigators are under a specific ethical obligation to use procedures “consistent with sound research design and that do not unnecessarily expose subjects to risk,” and to ensure that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”²¹⁹ Because this duty specifically requires assessing risks to the subjects, investigators should know the foreseeable risks they are imposing. Clinical research is like those situations where “the courts traditionally have allowed juries to deal more loosely with causation—the cases where the duty breached was one imposed to prevent the type of harm which plaintiff ultimately sustained.”²²⁰ If the study had not happened, then the subjects would not have lost a chance or been exposed to an increased risk of harm. It is not unfair to hold them liable for injuries resulting from those risks when they breach their duties to their subjects.

²¹⁷ Hodson, *supra* note 186, at 18.

²¹⁸ 445 So. 2d 1015, 1019–20 (Fla. 1984); see also *Cooper v. Sisters of Charity of Cincinnati, Inc.*, 272 N.E.2d 97, 103 (Ohio 1971) (stating that a lesser standard of proof “would be so loose that it would produce more injustice than justice”).

²¹⁹ 45 C.F.R. § 46.111 (2020); Emanuel et al., *supra* note 61, at 2705–06.

²²⁰ *Thompson v. Sun City Cmty. Hosp., Inc.*, 688 P.2d 605, 616 (Ariz. 1984).

Second, this objection derives much of its force from arguments dependent on relaxing the standard of proof in medical malpractice, which is viewed as subjecting physicians to a higher standard than other professions.²²¹ As discussed above, in clinical research cases, statistical analysis of the study results can show that the investigators caused harm to some of them by a preponderance of the evidence.²²² Thus, applying the lost chance model holds investigators liable for harms they have demonstrably caused. Holding them responsible for these harms is not holding investigators to a different standard than other professions. It is the only way to hold them to the same standard.

D. Towards a Theory of Marginal Causation

In the context of harms arising from clinical research, it is very nearly certain, especially relative to traditional proof requirements, that participation in the study caused an identifiable amount of harm. The main causation issue is that the specific harmed individuals cannot be identified. A defendant's negligence is certain to have caused some harm, but the circumstances make it impossible to determine which specific individuals were harmed. This situation is the mirror image of a classic torts problem in which two individuals independently, simultaneously and negligently act such that a plaintiff suffers an injury but cannot prove which individual caused the harm.

A variety of tort doctrines have developed for addressing the situation in which an injured plaintiff knows how he was injured but has difficulty proving the identity of the tortfeasor. The most prominent of these doctrines is alternative liability, which has its origin in the famous hunting accident occasioning *Summers v. Tice*.²²³ In that case, two hunters simultaneously and negligently shot a third member of their hunting party.²²⁴ It was certain that the plaintiff had suffered an injury, but because of the circumstances, he could not prove by the traditional standard of more-likely-than-not which of the two hunters had shot him.²²⁵ Despite being unable to prove traditional causation by a preponderance of the evidence, the court permitted the claim to go forward by shifting the

²²¹ See, e.g., *Kilpatrick v. Bryant*, 868 S.W.2d 594, 603 (Tenn. 1993).

²²² See supra Section III.B.

²²³ *Summers v. Tice*, 199 P.2d 1 (Cal. 1948).

²²⁴ *Id.* at 2.

²²⁵ *Id.* at 2–3.

burden of disproving causation onto the defendants.²²⁶ This ensured that the harmed plaintiff would be able to recover, while also preserving an opportunity for the defendants to exculpate themselves from liability.²²⁷

The related doctrine of market share liability, in which the burden shifts to defendants to prove that they could not have caused a plaintiff's injury after exposure to a fungible product, is justified because of similar difficulties in proving causation.²²⁸ In *Sindell v. Abbott Laboratories*, which dealt with *in utero* exposure to DES (diethylstilbestrol, a synthetic estrogen compound) that caused birth defects, the court had to determine whether a plaintiff could maintain a cause of action when she could not determine which drug maker had manufactured the DES she took.²²⁹ The court had to deal with the same thorny issue of causation: the plaintiff was harmed by DES, but there were "approximately 200 drug companies which made DES, any of which might have manufactured the injury-producing drug."²³⁰ After distinguishing *Summers* based on the fact that not every possible defendant had been joined, the court stated:

[W]e approach the issue of causation from a different perspective: we hold it to be reasonable in the present context to measure the likelihood that any of the defendants supplied the product which allegedly injured plaintiff by the percentage which the DES sold by each of them for the purpose of preventing miscarriage bears to the entire production of the drug sold by all for that purpose.²³¹

The *Sindell* court faced a situation in which the injury and the means of causing the injury were certain, but the identity of the tortfeasor could not be determined. Recognizing the wrongfulness of the plaintiff's otherwise-meritorious claim failing on these grounds, the court adopted a doctrine that allowed proportional recovery from tortfeasors whose collective wrongful conduct had contributed to the harm that the plaintiff suffered, even though the plaintiff could not demonstrate a specific causal link between any of the manufacturers and the specific pills she had taken.

Summers and *Sindell* show that normal causation analysis may sometimes be modified when it is certain that the defendant was complicit

²²⁶ *Id.* at 4.

²²⁷ *Id.* at 5.

²²⁸ *Sindell v. Abbott Lab'ys*, 607 P.2d 924, 936–37 (Cal. 1980).

²²⁹ *Id.* at 929–30.

²³⁰ *Id.* at 931.

²³¹ *Id.* at 937.

in causing an identifiable injury, but the circumstances make determining the specific actor difficult or impossible.²³² It is not always essential for plaintiffs to identify a specific chain of causation from the conduct of a specific defendant to the injury of a specific plaintiff. Instead, for market share liability, the injury is abstracted, with individual defendant liability being determined not by any actual causal chain, but by the probability that the defendant caused the injury as estimated by their relative market share.²³³

Like the harms suffered in market share liability by individual plaintiffs, clinical research data provide an evidentiary basis for concluding that some subjects have suffered an injury as a result of their participation in the study.²³⁴ Those injuries are directly attributable to the defendants who designed and conducted the study. What often cannot be pinned down is the specific identity of the subjects who suffered a negative outcome *and* incurred that result *because* of their participation in the study rather than because of the natural course of their health and treatment. This evidentiary issue, intrinsic to the circumstances, should not preclude the plaintiffs from establishing causation.²³⁵ Using the data generated from the study, courts should permit subject-plaintiffs to establish causation by showing the aggregate marginal injury the plaintiffs collectively have suffered as a result of participating in the study. Applying the same logic as the *Sindell* court, the value of these additional injuries should be proportionally distributed across the plaintiff-subjects who were in the worse-off group or groups and who experienced a negative outcome in the study.²³⁶ This would permit them

²³² *Summers*, 199 P.2d at 4; *Sindell*, 607 P.2d at 937.

²³³ *Brown v. Superior Ct.*, 751 P.2d 470, 487 (Cal. 1988) (stating that *Sindell* attempted to “achieve as close an approximation as possible between a DES manufacturer’s liability for damages and its individual responsibility for the injuries caused by the products it manufactured”).

²³⁴ For example, Dr. Beecher wrote about one study where, “[a]ccording to the data presented, 23 patients died in the course of this study who would not have been expected to succumb if they had received specific therapy.” Beecher, *supra* note 79, at 1356. This was a particularly egregious study in which the death rate for one group was almost three times higher than for the group receiving an intervention that had already been identified as superior in the literature. *Id.*

²³⁵ Cf. *Summers*, 199 P.2d 1 (Cal. 1948).

²³⁶ While this theory would mostly be litigated in a class action on behalf of the subjects, there is no reason why a court could not hear an individual claim under this theory and award the proportional damages individually. The class action vehicle is not itself a promising method for overcoming the traditional causation requirement. See Donald G. Gifford, *The*

to recover a portion of the damages attributable to the likelihood that each individual harmed subject was injured because they participated in the study. This is the basic proposal of marginal causation: when plaintiffs can show that a defendant inflicted some marginal aggregate harm on a defined class of vulnerable plaintiffs, but the circumstances make it impossible to show that any individual plaintiff was injured by the defendant's conduct or by the natural course of their vulnerability, courts should permit injured plaintiffs to recover for their injury discounted to the likelihood that the defendant's conduct caused it.

Marginal causation is a challenge to the traditional individual causation requirement of tort law, namely, that a specific defendant injured a specific plaintiff.²³⁷ Challenges to this requirement have focused on the identity of the defendant, because the specific injured plaintiff is bringing suit but cannot prove which defendants actually caused the injury.²³⁸ Judicial hesitation about elimination of the individual causation requirement is typically tied to the concern "that innocent defendants will be held liable for wrongs they did not commit."²³⁹ But this concern is entirely absent in clinical research, where the defendants are readily identifiable. No innocent defendant will unfairly be made to answer.

The idea of marginal causation also finds support in a recent decision by the Supreme Court. In *Paroline v. United States*, the Court grappled with a distinct but comparable problem of causation in the context of a federal criminal restitution statute.²⁴⁰ The statute at issue provided for criminal restitution to victims of child sexual exploitation or child pornography from convicted offenders.²⁴¹ The defendant in that case, Paroline, was convicted for possessing a victim's images, but there were likely thousands of other possessors of the same images.²⁴² After concluding that the statute required both proximate cause and cause-in-fact, the Court recognized that "a showing of but-for causation [could not] be made" because "Paroline was just one of thousands of anonymous possessors," and so "it [was] not possible to prove that [a victim's] losses

Challenge to the Individual Causation Requirement in Mass Products Torts, 62 Wash. & Lee L. Rev. 873, 895–98 (2005).

²³⁷ *Id.* at 875.

²³⁸ See *Sindell v. Abbott Lab'ys*, 607 P.2d 924, 926–31 (Cal. 1980).

²³⁹ *Thomas ex rel. Gramling v. Mallett*, 701 N.W.2d 523, 595 (Wis. 2005) (Prosser, J., dissenting).

²⁴⁰ *Paroline v. United States*, 572 U.S. 434 (2014).

²⁴¹ *Id.* at 443.

²⁴² *Id.* at 440–41.

would be less (and by how much) but for one possessor's individual role in the large, loosely connected network through which her images circulate.”²⁴³ To avoid this result, the Court considered the most-common less-demanding cause-in-fact tests.

These alternative causal tests are a kind of legal fiction or construct. If the conduct of a wrongdoer is neither necessary nor sufficient to produce an outcome, that conduct cannot in a strict sense be said to have caused the outcome. Nonetheless, tort law teaches that alternative and less demanding causal standards are necessary in certain circumstances to vindicate the law's purposes. It would be anomalous to turn away a person harmed by the combined acts of many wrongdoers simply because none of those wrongdoers alone caused the harm. And it would be nonsensical to adopt a rule whereby individuals hurt by the combined wrongful acts of many (and thus in many instances hurt more badly than otherwise) would have no redress, whereas individuals hurt by the acts of one person alone would have a remedy. Those are the principles that underlie the various aggregate causation tests the victim and the Government cite, and they are sound principles.²⁴⁴

The Court concluded that

[i]n this special context, where it can be shown both that a defendant possessed a victim's images and that a victim has outstanding losses caused by the continuing traffic in those images but where it is impossible to trace a particular amount of those losses to the individual defendant by recourse to a more traditional causal inquiry, a court . . . should order restitution in an amount that comports with the defendant's relative role in the causal process that underlies the victim's general losses.²⁴⁵

The test adopted by the Court is very similar to marginal causation. The basic differences are that, rather than there being many wrongdoers causing the harm, the defendants' conduct exacerbates the many prior

²⁴³ Id. at 448–50.

²⁴⁴ Id. at 452. In his dissent, Chief Justice Roberts takes issue with the application of these alternative causal tests to a federal statute. Id. at 467–72 (Roberts, C.J., dissenting). While it might be wrong to import a context-dependent causation into the federal statute at issue, common law courts face no such restriction when addressing claims for negligence in clinical research. And Chief Justice Roberts, describing the majority's causation inquiry as “sensible,” did not reject the propriety of alternative causation tests more generally. Id. at 463.

²⁴⁵ Id. at 458 (majority opinion).

causes that created the plaintiffs' vulnerabilities, and the marginal harm the defendants caused can only be measured across the plaintiffs as a group. As a result, "it is impossible to trace a particular amount" of the loss to the individual *plaintiff* "by recourse to a more traditional causal inquiry."²⁴⁶ So it makes sense that the remedy of marginal causation is broadly the same: a court should order damages "in an amount that comports with the defendant's relative role in the causal process that underlies the [plaintiff's] general loss[]."²⁴⁷

E. Liability and Recovery Under Each Theory

At this point, this Note has discussed three viable theories for proving causation in clinical research cases. First, there is the "compensable injury" theory, developed by Professor King, that permits recovery for lost chance as a separately compensable injury.²⁴⁸ Second, there is the "relaxed causation" theory, which would permit plaintiffs to prove causation by a lower standard than more-likely-than-not. Third, there is the novel marginal causation theory that determines the plaintiffs' aggregate marginal injury and allocates it to appropriate subjects with negative outcomes. As we will see, the application of the first two theories leads to plaintiffs being under-compensated and defendants being under-deterred.

The SUPPORT study provides an opportunity to apply these theories. The researchers in the SUPPORT study divided the subjects into two groups.²⁴⁹ Neither of these groups was properly a control group consisting of the typical therapeutic practice: there is no usual-care or best available therapy group to provide rigorous estimates of the but-for world. That should not impede the analysis because the defendant's negligence, which itself conceals the extent of the injury, should not permit them to escape liability.²⁵⁰ Because the investigators neglected to include a proper control group, the plaintiffs should be able to base their claims on inter-group

²⁴⁶ Id.

²⁴⁷ Id.

²⁴⁸ See King, *supra* note 152, at 1381.

²⁴⁹ SUPPORT Study, *supra* note 15, at 1961.

²⁵⁰ Cf. *Haft v. Lone Palm Hotel*, 478 P.2d 465, 475 (Cal. 1970) (shifting the burden of proximate cause to the defendant when the negligence deprived the plaintiffs of "a means of definitively establishing the facts leading to the [injury]").

comparisons between the high-oxygen treatment group and the low-oxygen treatment group.²⁵¹

According to the results of the study, the low-oxygen group experienced a death rate of 19.9%, while the high-oxygen group experienced a death rate of 16.2%.²⁵² Making the most favorable assumptions for the plaintiffs, the high-oxygen group's death rate should be applied to the low oxygen group, which produces 106 expected deaths, compared to 130 actual deaths.²⁵³ The study, therefore, produced about twenty-four additional deaths in the low oxygen group.²⁵⁴ The value of a statistical life used by the U.S. government, about ten million dollars, provides a reasonable estimate of the value of the lost lives.²⁵⁵ This is rounded to ten million dollars for simplicity. Using that value, the investigators caused about \$240 million of harm due to the negligent deaths of the twenty-four infants.²⁵⁶ The potential recovery for these deaths would be divided between the subjects who died. This would provide each of them with an 18.5% recovery on an entire wrongful death claim, or about \$1.85 million, which corresponds to the likelihood that they were the marginal subjects who died as a result of being in the low-oxygen group.²⁵⁷

²⁵¹ *Id.*; see also SUPPORT Study, *supra* note 15, at 1961.

²⁵² *Id.* at 1965.

²⁵³ 16.2% * 654 ≈ 106.

²⁵⁴ 130 – 106 = 24.

²⁵⁵ U.S. Dep't of Transp., Departmental Guidance on Valuation of a Statistical Life in Economic Analysis – 2016 Adjustment (Mar. 23, 2021), <https://www.transportation.gov/office-of-policy/transportation-policy/revised-departmental-guidance-on-valuation-of-a-statistical-life-in-economic-analysis> [https://perma.cc/M6EY-BTLZ].

²⁵⁶ \$10 million * 24 = \$240 million.

²⁵⁷ 24 ÷ 130 = 18.5%.

Theory	Compensable Injury	Relaxed Causation	Marginal Causation
Summary	Loss of chance compensated as a percentage of the total injury	Causation may still be satisfied when likelihood that negligence caused the injury is less than half	The aggregate marginal injury is divided between potentially injured plaintiffs
Hypothetical Harm	24 deaths	24 deaths	24 deaths
Value of a Statistical Life ²⁵⁸	\$10 million	\$10 million	\$10 million
Investigator Liability	\$48.1 million	\$48.1 million	\$240 million
Recovery for Deceased Plaintiffs	\$370,000	\$370,000	\$1.85 million

To see the difference between this marginal causation theory and the traditional loss of chance theory, consider how the *Herskovits* concurrence would treat this scenario. Taking the harmed plaintiff-subjects individually, the data suggest that each plaintiff in the low-oxygen group lost approximately a 3.7% percent chance of surviving.²⁵⁹ Applying King's proportional damages to this analysis suggests that each low-oxygen plaintiff that died should be able to recover 3.7% of their wrongful death claim, or \$370,000.²⁶⁰ But this would only provide a total recovery of \$48.1 million, totaling fewer than five aggregate wrongful deaths.²⁶¹ Hence, under the traditional method, plaintiffs collectively are made less than whole, relative to their expected lost chance, because the lost chance of the unharmed subjects is not counted towards the recovery of the harmed ones. This is not double counting for the harmed plaintiffs. Instead, it is the result of the fact that the lost chance, and the

²⁵⁸ U.S. Dep't of Transp., *supra* note 255.

²⁵⁹ $100\% - 16.2\% = 83.8\%$ (chance of survival in the high-oxygen group). $100\% - 19.9\% = 80.1\%$ (chance of survival in the low-oxygen group). $83.8\% - 80.1\% = 3.7\%$ (lost chance of survival for the low-oxygen group). Compare with *Herskovits*, in which the chance of surviving was diminished from 39% to 25%, resulting in a 14% lost chance. This decrease was found to be sufficient evidence of proximate cause for physician negligence. *Herskovits v. Grp. Health Coop. of Puget Sound*, 664 P.2d 474, 476–77 (Wash. 1983).

²⁶⁰ King, *supra* note 152, at 1381–83.

²⁶¹ 130 deceased subjects * 3.7% recovery * \$10 million = \$48.1 million.

compensation for it, is calculated based on the subjects as a class, but only a subset of that class is eligible for compensation.

Similarly, the relaxed standard of causation theory also provides an unsatisfactory result. Most courts in applying the reduced causation standard derived from *Hicks* have limited damages to the amount of chance lost as a result of the negligence.²⁶² That makes the result mathematically indistinguishable from Professor King's theory, with just \$370,000 in damages for the deceased plaintiffs. Without marginal causation, the defendant-researchers will be under-deterring from carrying out negligent research. And although plaintiffs can never be perfectly compensated because of the epistemological impossibility of observing the counterfactual world, marginal causation better satisfies the corrective-justice function of tort law by at least providing more compensation to the actually harmed plaintiffs.

CONCLUSION

Ensuring that there are proper protections in place for human subjects is a vital component of safeguarding the ethics of clinical research. The medical and scientific communities and federal government regulations provide for some protection through self-policing.²⁶³ But these institutions have few incentives, other than their sense of propriety and the need to protect federal funding by appearing to comply with federal regulations, to thoroughly investigate and vet proposed research studies.²⁶⁴ The individuals with the most on the line, who have the highest incentives to speak out against investigator misconduct, are the subjects imperiled by a negligent study. Subjects who believe that they have been wronged as a result of participation in a study should be able to seek recourse through the courts. There is a clear consensus among ethicists that investigators owe important ethical duties to their subjects.²⁶⁵ Courts should reckon with these duties and permit subjects to enforce them, like most persons experiencing a serious harm caused by another, by bringing claims against the tortfeasors who wronged them. History

²⁶² See *Mays v. United States*, 608 F. Supp. 1476, 1482–83 (D. Colo. 1985), rev'd on other grounds, 806 F.2d 976 (10th Cir. 1986); see also *James v. United States*, 483 F. Supp. 581, 587 (N.D. Cal. 1980); *O'Brien v. Stover*, 443 F.2d 1013, 1019 (8th Cir. 1971).

²⁶³ See supra Section II.B.

²⁶⁴ See Annas & Annas, supra note 41, at 45.

²⁶⁵ See supra Section II.C.

overwhelmingly testifies to the risks arising when investigators experimenting on human subjects are not held to account.²⁶⁶

The demands of traditional causation, developed for general application to a wide variety of cases, should not be the sole reason that harmed research subjects fail to receive recognition from the law. When harms arise from clinical research, it is often clear from the data that the study has caused harm to some subjects. Causation becomes a central issue in these cases because, in the typical clinical research study, the procedures, method, and study design conspire to make it difficult or impossible to prove the identity of the harmed subjects or the extent to which any individual subject was harmed. The most straightforward approach to rectify this issue, which bars otherwise meritorious claims, is to recognize the parallels to medical malpractice and apply the loss of chance doctrine to clinical research.²⁶⁷ Because the circumstances of clinical research make it possible to show loss of chance with a degree of rigor that is often impossible in medical malpractice, even courts that reject loss of chance in medical malpractice should accept it for clinical research.²⁶⁸ In light of the circumstances of clinical research, courts should consider whether a new doctrine, tailored to the indeterminate identity of the specific plaintiffs, should be applied to clinical research. Such a doctrine, which this Note has termed marginal causation, would effectively be an extension of the alternative liability and market share liability doctrines.²⁶⁹

There is an important role for courts to play in regulating the relationship between human subjects and researchers. Common law courts have often interposed themselves in relationships where there is a potential for unfairness or oppression. The courts should take their rightful place as bastions against the unethical conduct that can so easily arise when investigators—even well-meaning ones—treat their subjects as mere means and negligently ignore their ethical and legal duties in pursuit of scientific ends.

²⁶⁶ See supra Section II.B.

²⁶⁷ See supra Section III.B.

²⁶⁸ See supra Section III.C.

²⁶⁹ See supra Section III.D.