

Research Science, Ethics and Litigation

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Disclosures:

- Associate Editor: New England Journal of Medicine
- Section Editor: UpToDate
- Editor: Creasy & Resnik's Maternal Fetal Medicine
- Editor: deSwiet's Medical Disorders in Obstetric Practice
-

“Biomedical research, no matter how well designed, and ethically conducted, carries uncertainties and exposes participants to risk of injury.”

New York Times Nov 28, 1999



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The Biotech Death of Jesse Gelsinger

By SHERYL GAY STOLBERG NOV. 28, 1999

"What's the worst that can happen to me?" he told a friend shortly before he left for the Penn hospital, in Philadelphia. "I die, and it's for the babies."

Paul Gelsinger, Jesse's father



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- “I've never been more proud of my son than the moment he decided to do this experiment.”
- “Too many mistakes had been made and unfortunately, because of our litigious society, it was the only way to correct these problems.”

NEJM 2006;355:1018



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The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P.,
Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A.,
Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

NEJM 2010 (27May)



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SUPPORT Study

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

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Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

SUPPORT NEJM 2010;362:1959



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Table 2. Major Outcomes.*

Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	<i>no./total no. (%)</i>		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76-1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37-0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01-1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99-1.63)

SUPPORT NEJM 2010;362:1959



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CONCLUSIONS

A lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern, since a lower target range of oxygen saturation is increasingly being advocated to prevent retinopathy of prematurity. (ClinicalTrials.gov number, NCT00233324.)



Medical Study Put Premature Babies at Risk

By Sam Jewler

In early April, Public Citizen exposed to the world a highly unethical, federally funded experiment that, between 2005 and 2009, put more than 1,300 prematurely born infants at increased risk of blindness, brain injury or death, without adequate informed consent from their parents.

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), which was conducted by a group of prestigious medical schools and research institutions including

those at Stanford and Yale, randomly divided prematurely born infants — born as early as six months into the pregnancy, at an average weight of around two pounds — into two experimental groups. For one group, the researchers tried to maintain the infants' blood oxygen levels in a low target range and, for the other group, in a high target range — rather than adjust each one's oxygen levels within the usual recommended broader range to meet his or her individual needs. The researchers then measured the impact of the different rang-

es of oxygen levels for premature babies — specifically whether infants in one group were more likely to die or develop a serious eye disease that could lead to blindness in comparison to the other group. But the risks of this oxygen experiment were not made known to the parents signing their babies up for the randomized experiment.

Prematurely born babies generally need oxygen support to survive, and more than 50 years of medical research has demonstrated that, for premature babies, a lack of oxygen can cause

brain injury or death, whereas too much oxygen can lead to blindness. Indeed, the results of this study showed that infants in the high-oxygen group were twice as likely to develop the serious eye disease associated with prematurity as those in the low-oxygen group — 18 percent versus 9 percent. Not surprisingly, babies in the low-oxygen group had a higher death rate, with 20 percent of babies in that group dying before discharge compared to 16 percent in the high-oxygen group.

see Babies , page 4



In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

Each year in the United States, nearly 500,000 infants — 1 in every 8 — are born prematurely, before 37 weeks of gestation. Despite substantial advances in their care, premature infants face

a daunting array of challenges; they are at high risk for death in infancy and face severe and life-long health problems if they survive.¹ The National Institutes of Health (NIH) has a legal and

moral responsibility to do research in partnership with scientists and families to optimize the care of these highly vulnerable infants. In recent weeks, a major public debate has arisen regarding a



LOONEY V. MOORE, Case No.: 2:13-cv-00733-KOB (N.D. Ala. Aug 13, 2015)

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

LOONEY V. MOORE

Case No.: 2:13-cv-00733-KOB (N.D. Ala. Aug 13, 2015)

N.D. Ala.

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF
ALABAMA SOUTHERN DIVISION

Case No.: 2:13-cv-00733-KOB

08-13-2015

BILLY RYAN LOONEY, ET AL.,
Plaintiffs, v. SHEILA D MOORE, ET AL.,
Defendants.

KARON OWEN BOWDRE CHIEF
UNITED STATES DISTRICT JUDGE

the UAB Institutional Review Board ("IRB Defendants"),¹ the board that approved the SUPPORT study at UAB. (Claims I-IX). The Plaintiffs also assert claims for negligence, breach of fiduciary duty, and lack of informed consent against Dr. Waldemar Carlo, who served as the principal investigator for the research trial and designed the trial's protocols. (Claims X-XII). Finally, the Plaintiffs assert claims for products liability and negligence against the Masimo Corporation, which manufactured modified pulse oximeters² that were used in the study. (Claims XIII-XIV).

1. The following individual Defendants comprise the Institutional Review Board: Sheila D. Moore, Ferdinand Urthaler, Kenneth Pruitt, John Carpenter, Mary Hilliard, Richard Parker, William Blackerby, Marguerite Kinney, Matthew Doss, Charles Russell, and Daniel

“For the reasons discussed below, this court will grant all of the Defendants' motions for summary judgment. Additionally, because the Defendants are entitled to summary judgment regardless of the dispositions of the motions to strike, the court will deny those motions as moot.”

Compensation for subjects injured in research trials



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- Despite extensive federal regulations to protect research subjects from risks;
 - Risk minimization strategies
 - Informed consent process
 - Institutional Review Board
 - Data Safety and Monitoring Board
- There is no legal requirement to care for or financially compensate participants who suffer research related injuries



Characteristics of 129 Policies for Injuries to Research Volunteers at 102 Academic Medical Centers in the United States.

Policy Provision	Policies <i>no. (%)</i>
Free care not provided	66 (51.2)
Medical treatment billed at usual and customary fees	54
Emergency or immediate treatment billed at usual and customary fees	12
Free care provided	21 (16.3)
Medical treatment	10
Emergency or immediate care	11
Care billed to insurance first but free for those without insurance	13 (10.1)
Medical treatment	9
Emergency or immediate care	4
Care billed on a case-by-case basis	5 (3.9)
No publicly accessible information	24 (18.6)

Compensation for subjects injured in research trials



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- Recognizing this problem in 2002, the Institute of Medicine recommended: “organizations conducting research should compensate any research participant who is injured as a direct result of participating in research, without regard to fault. Compensation should include at least the costs of medical care and rehabilitation, and accrediting bodies should include such compensation as a requirement of accreditation.”

Compensation for subjects injured in research trials



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- In most of Europe there is universal healthcare, which fundamentally changes subjects' concern about medical expenses incurred due to injuries in a trial.
- The 2001 European directive on the conduct of clinical trials states that a trial may be undertaken only if “provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.”
- Some countries, such as France, Germany, and Spain, have compulsory insurance laws, although there is variation in the specifics and in the minimum coverage that is required.

Options for Compensation for subjects injured in research trials



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- The National Vaccine Injury Compensation Program, since 1988, a no-fault alternative to the traditional tort system for resolving vaccine injury claims. Covers all vaccines recommended by the CDC for routine administration to children.
- A nationwide compensation fund analogous to the September 11 Victim Compensation Fund.
- Enactment of a legal requirement compelling research institutions and/or research sponsors to either purchase insurance or self-insure against research participant injuries.

- The University of Washington is one institution with a longstanding compensation plan. The university's self-insured, no-fault plan dates from the 1970s. It covers medical expenses associated with adverse events and some incidental expenses, such as travel and child care. The division of financial responsibility between commercial sponsors and the university is specified in negotiated agreements. The university typically has one or two claims per year, and it writes off the cost of in-house medical expenses.

Compensation for subjects injured in research trials



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- U.S. institutions with policies that offer medical care to participants who suffer research related injuries in agency conducted clinical trials:
 - Department of Veterans Affairs
 - Department of Defense
 - National Institutes of Health Clinical Center
 - Medicare covers some trial related injuries

Injured subjects resort to the “Legal Lottery”



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- The vast majority of subjects injured in research trials are forced to resort to the tort system.
- An adversarial system where injured subjects can rarely meet the financial and evidentiary burdens of a successful claim. (Class action law suits)
- The few plaintiffs who prevail usually do so on the basis of facts demonstrating deficient informed consent, investigator conflict of interest or fraud.
- For the vast majority of injured participants the tort system is costly, lengthy, and yields no remedy.



ACADEMIA AND CLINIC

The Rise of Litigation in Human Subjects Research

Michelle M. Mello, JD, PhD, MPhil; David M. Studdert, LLB, ScD, MPH; and Troyen A. Brennan, MD, JD, MPH

Owing to widespread public concern about the adequacy of protections for human research subjects and recent instances of serious injury to subjects at several major research institutions, lawsuits against investigators, institutional review boards, and academic institutions are becoming increasingly common. Several claim-promoting conditions are ripe to promote the further growth of this litigation and raise the stakes for research institutions. While this litigation may serve a valuable compensation function

for injured subjects, it will also have profound effects on institutional review boards, leading to a more legalistic, mechanistic approach to ethical review that does not further the interests of human subjects or scientific progress.

Ann Intern Med. 2003;139:40-45.

For author affiliations, see end of text.

See editorial comment on pp 71-72 and Letter on p 77.

www.annals.org

- While this litigation is inefficient and will increase the costs of doing research, “it may serve a valuable compensation function for injured subjects, [but it] will also have profound effects on institutional review boards, leading to a more legalistic, mechanistic approach to ethical review that does not further the interests of human subjects or scientific progress.”

Injured subjects resort to the “Legal Lottery”



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- An award for injuries through the tort system requires findings of “fault” and causation.
- Both of these elements can be difficult to demonstrate in the setting of a clinical trial.
- Is the adverse outcome due to “injury”, “failure to rescue”, or a well known, if uncommon occurrence?
- Well conducted research can and does occasionally result in injuries in the absence of negligence or wrongdoing, which is precisely why these experiments are necessary.

Conclusions



- The current system does not work well for anyone; research subjects, investigators or sponsoring agencies.
- For research subjects, an ideal system would provide no fault coverage for the costs of treatment for injuries, transportation, child care, lost wages, promptly, efficiently and at low cost to the system. Who should pay?
- Investigators and sponsoring institutions who act in good faith within the current research regulatory framework of IRBs, DSMBs, etc. should, in theory, be largely protected from lawsuits by a system that eliminates incentives to resort to the tort system for remedies.