Testimony to HHS
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Profs. Dreger and Reverby were co-signers on the June 26, 2013 letter published by the *New England Journal of Medicine* agreeing with OHRP's findings in the SUPPORT study.[1]

We speak to you today as historians of medicine and human subjects' research, very much concerned with the present and future of medicine and medical research. We seek to provide historical context to today's discussion and to make specific recommendations based on the long-view.

We begin with some historical perspective.

As many of you know, almost 50 years ago, in 1966, Henry K. Beecher published his now-famous review in the *New England Journal of Medicine* called "Ethics and Clinical Research."[2] Beecher reviewed a large number of clinical studies occurring at "leading medical schools, university hospitals" and "governmental institutes," including the National Institutes of Health. He showed that the American medical research system was rife with ethical missteps and outright abuses, concluding: "ethical errors are increasing not only in numbers but in variety." In other words, by 1966, ethical problems within medical research appeared endemic.

Beecher's analysis suggested that the etiology of the problem lay in a skewed professional milieu that today has become even more problematic. Although individual medical researchers are *motivated* by a beneficent desire to preserve health and save lives, what is *rewarded* in medical research is ever more scholarly production, not a nuanced understanding of what counts as ethical behavior in research. Indeed, in today's academic climate, researchers who attempt to be ethically meticulous may find themselves effectively *punished* through delays, lower enrollment, and thus failure to compete. In other words, the American medical research system is still set up to allow these ethics problems to keep happening. It may even *promote* ethical shortcuts and missteps, just as Beecher noted nearly four decades ago.

Unlike in Beecher's time, today there are Institutional Review Boards (IRBs), dedicated local bodies designed to prevent research ethics mistakes. We also have OHRP as a federal regulatory office to investigate complaints of wrongdoing. However, day-to-day local pressures on academic researchers to take ethical shortcuts, even when they think that is not what they are doing, may well overwhelm the needs and rights of potential subjects. That OHRP has been successfully pushed into backing off on enforcement of its criticisms of the SUPPORT

trial[3] suggests again that, in contemporary American medical research, attempts to hold researchers to the highest ethical standards will be seen as overly intrusive, sometimes even as a threat to medical progress.[4] With a documented decline in actions by the OHRP over the last several years[5] and now the OHRP apparently backing off on enforcement in the SUPPORT trial, the federal office designed to protect the rights and welfare of patients who become subjects appear to be growing weaker and weaker at a time when more and more patients are being turned into subjects.

Because we think the SUPPORT study may represent the tip of the iceberg with the problems in contemporary medical research—and because it involved approximately 23 medical centers, their IRBs, and the NIH—the SUPPORT study is a useful case to examine. Let us acknowledge outright that OHRP was right in its findings on the SUPPORT study;[6] as stated in the letter we signed with 43 colleagues to the *New England Journal of Medicine*, "the informed-consent documents that were used in the [SUPPORT study] were seriously inadequate."[7] Here, as so many times in the history of American medical research, the consent process failed. We fully expect that, if Beecher were alive, and re-doing his study today, he would find many problematic contemporary studies, including the SUPPORT study. That is exactly why we need OHRP's enforcement to stand, and why we continue to need external eyes on research trials.

In the specific case of the SUPPORT trial, most egregiously, about half of the study consent forms described the trial's interventions as "standard of care."[8] This nomenclature seems to have been designed to reassure parents who might enroll their very premature babies that it would have made no real difference whether or not they enrolled. As the OHRP found, parents should have been told that randomization into restricted trial arms in this study could potentially increase (or decrease) the odds that their babies would suffer death and particular impairments. The protocol and publications show that the study was designed to determine just those risks. Consent was so poorly handled in this trial, OHRP should have required—and should *still* require—that the involved institutions now inform parents what they should have been told before enrollment—that being in the

SUPPORT study was likely to have changed how their baby was treated in the neonatal intensive care unit (NICU) and might have increased the risk of death and disability. It feels wrong that we are having this conversation still without the parents having been so informed.

The major ethical problem with the SUPPORT study amounts to a classic problem of informed consent, reminiscent of so many of the problem cases Beecher found and so many cases we teach in medical history and ethics. If the best clinical judgment in NICUs was not evidence-based because we lacked the data the SUPPORT study was designed to generate, then *the parents needed to be told that*, not have the decision of which set of risks to assume be made by clinician-researchers In the SUPPORT study. It should have been up the *parents* to decide whether to take on the risks of randomization into controlled research arms, or to instead have their babies' care based on the best clinical judgment of the NICU staff. A physician is never exempt from disclosing the risks associated with so-called "standard of care" interventions, whether the patient becomes a subject or not.

One cannot justify failure to tell the parents of the potential risks with the claim "until the study was done, we couldn't know for sure the risks." [9] Even if the same range of risks existed in ordinary NICU care, parents needed to understand their baby might be subject to a *different* subset of risk odds, and ultimately a different set of harms, via enrollment into this randomized clinical trial (RCT). The consent forms for the SUPPORT trial should have explained what care outside the trial would look like, and what risks were associated with that care. An honest conversation about risk should never be made to go away by calling something "standard of care."

We are also alarmed that pregnant women and their partners were asked to consider enrollment of their babies in this study just at the moment when those women were facing the very premature birth of their child. It is not clear to us that any mother, or her partner, in such a situation could have the mental wherewithal to seriously consider enrollment of their extremely premature baby in a major trial, particularly one that might change risks of death or disability. We hasten to remind those here that, much as we would dearly love data on certain interventions, there

are sometimes trials that simply cannot be done ethically. IRBs looking at applications from the SUPPORT study researchers should have been extremely concerned about how enrollment into an RCT of this nature could be done more ethically. It would have helped to have some kind of qualitative research done first on how parents respond best to risk assessment in a NICU before this study was done.

Given the somewhat shocking inadequacies of its consent processes, the SUPPORT trial should be understood as evidence that the use of decentralized local IRBs in a multi-site study fails to produce a redundancy that increases protection of subjects. It suggests that a centralized IRB without internal competing institutional interests might be safer for subjects, as bioethicist Jay Katz argued decades ago.[10] Most obviously, it suggests that local IRBs are failing to catch basic mistakes, such as describing randomized controlled research interventions as equivalent to "standard of care." That top NIH officials would criticize the OHRP for pointing out these basic ethical errors is worrisome indeed.[11]

Make no mistake: We are enthusiastically in favor of good clinical research, even on premature babies. But such research, which has the potential to benefit the whole of society, cannot be done at the expense of the rights of the vulnerable individuals used as subjects and, in this case, the rights of their parents as well.

This meeting is being held under the pretense that the confusion over informed consent in the SUPPORT trial occurred because of the supposedly special ethical aspects of a trial aimed at testing one kind of common intervention against another. Not only do we insist that existing OHRP regulations are absolutely adequate for the management of trials involving commonly-used medical interventions as well as trials like SUPPORT, we also must insist that discussing the SUPPORT trial as a case of so-called "standard of care research" is just plain wrong. Several of the experimental interventions in the SUPPORT study did not represent commonly used clinical interventions.[12] For example, we are unaware of any NICU that would carefully seek to maintain a very premature baby at an oxygen saturation level of 85-89% regardless of the baby's clinical status, as happened to babies in one arm of the oxygen saturation intervention. We are unaware of any

NICU that would regularly withhold surfactant from very premature babies. Surfactant is a treatment widely believed to make an enormous difference in survivability of extreme prematurity. We are also unaware of NICUs where practitioners would, outside of research, be blinded as to the real oxygen saturation levels of children they are treating.

Scholars have long noted the problem of the "therapeutic misconception," i.e., when one "den[ies] the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself.".[13] The SUPPORT study consent documents seem at times to have actively promoted the therapeutic misconception; it appears indeed that some of the clinical researchers were themselves laboring under this misconception. That so many clinicians—and, strangely, a few ethicists—have continued to insist that enrollment in SUPPORT meant receiving "standard of care"[14] suggests to us a real failure to understand the difference between medical treatment and medical research.[15]

Those who have called for a new ethics framework for what is being labeled a "learning health care system"—in which essentially every patient becomes a subject—acknowledge that the lines between clinical practice and clinical research can sometimes be unclear.[16] Even these ethicists argue, however, that clinician researchers have an "obligation to provide optimal care to each patient."[17] Further, we do not think, as some have said, that "patients have an obligation to contribute to, participate, or otherwise facilitate learning"[18] in a situation where they were not given a chance to consent to the risks involved in what they were told was a "standard of care" clinical trial with supposed clinical equipoise.

Again, we insist that the problem here is not that the regulations as they currently exist provide inadequate guidance for RCTs that include trial arms that really do reflect interventions one would be quite likely to receive in a clinic as a patient. The problem here isn't fuzzy regulations: the problem here is fuzzy thinking about those regulations as pressure to enroll patients as subjects is at an all-time high. The problem here is the slippage occurring as researchers think "patient equals subject equals patient"[19]—a problem codes like Nuremberg, the declarations

from the WMA in Helsinki, and regulations like the Common Rule are primarily meant to forestall.

Some have claimed that the move towards more evidence-based medicine—towards so-called "precision medicine"[20] or towards a so-called "learning health care system," in which essentially every patient becomes a subject[21]—requires a system where the line between patient and research subject necessarily becomes blurry. We strongly object to this idea, and warn you that this type of reasoning has been used again and again—including in the Tuskegee Syphilis Study—as a way for researchers to justify non-consented, or poorly consented, risky research on unsuspecting subjects who thought they were just patients. Although we are not saying the SUPPORT study is akin to the Tuskegee Study, and we would discourage overusing that study as a metaphor, we should remember that the Tuskegee Study was in many ways understood to be a kind of "standard of care" research because, the researchers said, the men in the study were not going to get adequate treatment for their syphilis anyway, so why not study what happened to them if they were left untreated? And then, when adequate treatment did become generally available, the men in the study were to be kept at the assumed "standard of care": the assumed no treatment.[22] But now, as then, the road to better evidence-based medicine ought never be paved with the bodies of ill-informed subjects. We cannot allow physicians to slip into a mode where they fail to remain vividly conscious of the differences between patients and subjects.

Patients must not be made into subjects without truly informed consent, no matter how much we try to convince ourselves that enrollment in a study is not really different from what a particular patient will experience in ordinary clinical care. We understand that it would be good, in theory, to have data from every clinical encounter gathered and used scientifically ultimately to improve patient care. Nevertheless, we know how humans work: we know that once a physician starts to act as a researcher by using patients for research data collection, her or his mind will be approaching that individual as a research subject. We might indeed have a *reverse* of what social scientists in 1950 began to call the Hawthorne effect:

where the researchers/doctors now change how they treat their patients because they know their patients are, in fact, in a research study.

We want to be especially clear about one thing: We are not calling the SUPPORT researchers (or the members of the IRBs that approved their study) or other American medical researchers evil or thoughtless, or even intentionally unethical. Frankly, this situation would be simple if what we were dealing with were a few bad eggs who could be isolated and routed out. As Beecher understood, well-intentioned researchers, often people at the tops of their fields, have been responsible for much of the ethical mischief committed in medical research. Ethical missteps happen not because most researchers become "Nazis" deployed by an evil state, or greedy researchers employed by Big Pharma, or self-centered egomaniacs. Ethical problems happen because of the tremendous intrinsic and extrinsic pressures on American clinical-researchers and also their IRBs to get people enrolled in studies, get data out of the studies, and because of the belief in the good for science that will come from the research.

Until medical professionals realize that "the road to hell is paved with good intentions"—until they truly *believe* that good people can unthinkingly do bad things in the course of every-day work—we will continue to see the same mistakes happening. We will continue to ritualistically meet like this to express shock at how this has happened again. We will fail to see the irony of how this kind of "cathartic" event such as today's hearing of possible scandal and punishment keeps the same dangerous system in place.[23] Until doctors who are also clinical researchers have the humility to realize their potential to do harm while meaning to do good, the same problems will keep arising.[24] Until we see how we have created an environment that fosters ethical mistakes, and that openly resists enforcement when mistakes are found, the same problems will keep arising.[25]

As historians, we can tell you, there is nothing magically different about today's technologically-advanced, multi-center clinical trials like the SUPPORT study that makes them exempt from the codes and regulations already devised. We are not in a new era ethically speaking. There was nothing about the Department of Health and Human Services (HHS) regulations enforced by OHRP that should or

could have allowed confusion as to what needed to happen with the SUPPORT trial. We are dealing here with a new version of same-old problems of failing to adequately inform and to adequately protect the rights of extremely vulnerable populations who become medical research subjects. We are here again to have the same conversation we have been having for generations about failure to obtain appropriate informed consent. It is a conversation worth having, but we should not pretend it is new.

Based on the foregoing analysis, we make the following recommendations to HHS, OHRP, the NIH, and institutional IRBs:

1. The case of SUPPORT should *not* be used to discuss research on interventions that are commonly understood to be "standard of care," because several of its experimental interventions would have to be called clinically peculiar if not clinically non-existent.

2. The use of the phrase "standard of care" in clinical medicine or clinical research does not exempt a physician or researcher from an honest discussion of risks with patients and subjects before obtaining consent.

3. We must all recognize that there are some studies that cannot ethically be done, much as we want the data they could produce. More qualitative research is needed in the future to explore how NICU parents can be ethically informed about risks and asked to join research studies.

4. OHRP and HHS should require extraordinary proof before accepting any claim that today's forms of research require revised regulations or new interpretations of regulations as we move toward what some are calling a "learning health care system." Existing regulation is adequate to modern research forms and should not be weakened in the name of promoting science and patient care.

5. Vigorous enforcement of existing regulations is needed and should be supported, not hampered. The successful political pressure from NIH and researchers that has forced OHRP to back off its enforcement actions in the SUPPORT trial should be understood as extremely alarming. It suggests that any revision of existing regulations at this political moment may well result in *weakened* protections for subjects.

6. Parents who agreed to enroll their children in the SUPPORT study should be informed of the OHRP's findings.

7. IRBs and clinical researchers should be better educated as to how existing human subjects regulations already apply to various types of study.

8. The SUPPORT trial should be understood as evidence that the use of decentralized local IRBs in a multi-site study fails to produce a redundancy that increases protection of subjects.

9. The SUPPORT trial should not be understood as a sensational story of bad and good, but rather should be understood as another classic case of failure of informed consent committed by well-intentioned eager researchers, focused on the greater good, driven by a problematic reward and punishment system.

10. We should all acknowledge that the system continues to reward grants and publications, not ethically meticulous care of subjects. In fact, being ethically meticulous makes it *harder* for a researcher to compete in the existing reward systems. Thus we should all understand that the system is set up more to foster than to prevent these kinds of ethical failures. Enforcement in cases of wrongdoing and active rewards for meticulous ethical behavior are critical to producing ethical behavior.

In conclusion, we do not think any bureaucratic system can perfectly prevent more cases like the SUPPORT study from happening. The only real protection against these situations involves a combination of extreme humility, the constant attention of the uninvolved (because the uninvolved have less at stake and so less complicated vision), and a genuine willingness on the part of individual researchers and institutional administrators to lose in the research game, if losing is what it takes to put ethics first.

Notes:

[1] Ruth Macklin, Lois Shepherd, Alice Dreger, Adrienne Asch, Francoise Baylis, Howard Brody, Larry R. Churchill, Carl H. Coleman, Ethan Cowan, Janet Dolgin, Jocelyn Downie, Rebecca Dresser, Carl Elliott, M. Carmela Epright, Ellen K. Feder, Leonard H. Glantz, Michael A. Grodin, William Hoffman, Barry Hoffmaster, David Hunter, Ana S. Iltis, Jonathan D. Kahn, Nancy M. P. King, Rory Kraft, Rebecca Kukla, Lewis Leavitt, Susan E. Lederer, Trudo Lemmens, Hilde Lindemann, Mary Faith Marshall, Jon F. Merz, Frances H. Miller, Margaret E. Mohrmann, Haavi Morreim, Meryl Nass, James L. Nelson, John H. Noble, Elizabeth Reis, Susan M. Reverby, Anita Silvers, Aron C. Sousa, Roy G. Spence, Jr., Carson Strong, Judity P. Swazey, and Leigh Turner, "The OHRP and SUPPORT—Another View," *NEJM*, vol. 369, no. e3 (July 11, 2013), at http://www.nejm.org/doi/full/10.1056/NEJMc1308015.

[2] Henry K. Beecher, "Ethics and Clinical Research," *NEJM*, vol. 274, no. 25 (June 16, 1966): 1354-60.

[3] Teresa Defino, "'SUPPORT' Backlash Prompts Meeting, Guidance as Debate Moves Beyond OHRP," *Report on Research Compliance*, vol. 10, no. 7 (July 2013): 1-5, at http://www.reportonresearchcompliance.com/rrc-reprint-0713.pdf; see also Lisa R. Buchanan for the OHRP, letter to Richard B. Marchase for the University of Alabama at Birmingham, June 4, 2013, at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf.

[4] See, e.g., Benjamin S. Wilfond, David Magnus, Armand H. Antommaria, Paul Appelbaum, Judy Aschner, Keith J. Barrington, Tom Beauchamp, Renee D. Boss, Wylie Burke, Arthur L. Caplan, Alexander M. Capron, Mildred Cho, Ellen Wright Clayton, F. Sessions Cole, Brian A. Darlow, Douglas Diekema, Ruth R. Faden, Chris Feudtner, Joseph J. Fins, Norman C. Fost, Joel Frader, D. Micah Hester, Annie Janvier, Steven Joffe, Jeffrey Kahn, Nancy E. Kass, Eric Kodish, John D. Lantos, Laurence McCullough, Ross McKinney, Jr., William Meadow, P. Pearl O'Rourke, Kathleen E. Powderly, DeWayne M. Pursley, Lainie Friedman Ross, Sadath Sayeed, Richard R. Sharp, Jeremy Sugarman, William O. Tarnow-Mordi, Holly Taylor, Tom Tomlinson, Robert D. Truog, Yoram T. Unguru, Kathryn L. Weise, David Woodrum, Stuart Youngner, "The OHRP and SUPPORT," *NEJM* vol. 368, no. e36 (June 20, 2013), at http://www.nejm.org/doi/full/10.1056/NEJMc1307008.

[5] Teresa Defino, "Big Drop in OHRP Letters, Open Cases Raise Questions of Agency Commitment," *Report on Research Compliance*, vol. 8, no. 3 (March 2011): 1-3, at http://www.reportonresearchcompliance.com/rrc0311_reprint.pdf.

[6] Lisa R. Buchanan for the OHRP, letter to Richard B. Marchase for the University of Alabama at Birmingham, March 7, 2013, at http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf.

[7] Macklin, Shepherd, Dreger, et al., "The OHRP and SUPPORT—Another View" (see note 1 above).

[8] Michael Carome and Sidney Wolfe, "The SUPPORT Study was Even Worse than We Thought," *Bioethics Forum* (May 21, 2013), at http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6367&blogid=140; see also Michael A. Carome, Sidney M. Wolfe, and Ruth Macklin for Public Citizen,

letter to Kathleen Sebelius for the Department of Health and Human Services, May 8, 2013, at http://www.citizen.org/documents/2124.pdf. Public Citizen has obtained and made available all of the consent forms at: http://www.citizen.org/documents/support-study-consent-form.pdf

[9] See Jeffrey M. Drazen, Caren G. Solomon, and Michael F. Greene, "Informed Consent and SUPPORT," NEJM, vol. 368 (May 16, 2013): 1929-31, at http://www.nejm.org/doi/full/10.1056/NEJMe1304996; and John D. Lantos, "Public Citizen and Misinformed Consent in Neonatal Intensive Care," *Bioethics Forum* (May 16, 2013), at http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6357&blogid=140.

[10] Jay Katz, "Human Experimentation and Human Rights," *St. Louis University Law Journal* 38 (1993): 7-54.

[11] Kathy L. Hudson, Alan E. Guttmacher, and Francis S. Collins, "In Support of SUPPORT—A View from the NIH," *NEJM*, vol. 368 (June 20, 2013): 2349-51, at http://www.nejm.org/doi/full/10.1056/NEJMp1306986.

[12] Protocol for NICHD Neonatal Research Network, "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" (March 28, 2005), at http://www.nih.gov/icd/od/foia/library/Protocol.pdf

[13] P.S. Appelbaum et al., "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," *Hastings Center Report*, vol. 17, no. 2 (1987): 20-24.

[14] See, for example, John D. Lantos, "Public Citizen and Misinformed Consent in Neonatal Intensive Care," *Bioethics Forum* (May 16, 2013), at http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6357&blogid=140

[15] See F. G. Miller and Howard Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *Hastings Center Report*, vol. 33, no. 3 (May-June 2003): 19-28; note that there was not really clinical equipoise in the SUPPORT trial.

[16] Ruth R. Faden et. al., "An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research and Clinical Ethics," *Hastings Center Report* 43 (2013): S16-S27.

[17] Faden et al., p. S21.

[18] Faden et al., p. S22.

[19] Susan M. Reverby, *Examining Tuskegee: The Infamous Syphilis Study and its Legacy* (Chapel Hill: University of North Carolina Press, 2009, 2013).

[20] National Research Council Committee on a Framework for Developing a New Taxonomy of Disease, *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (Washington: National Academies Press, 2011).

[21] Faden et al.

[22] Reverby, *Examining Tuskegee*; see also Susan M. Reverby, ed. *Tuskegee's Truths* (Chapel Hill: University of North Carolina Press, 2000).

[23] Carlo Ginzburg, The Judge and the Historian (London: Verso, 1991), p. 73-74.

[24] Susan M. Reverby, "Ethical Failures and History Lessons: The U.S. Public Health Service Research Studies in Tuskegee and Guatemala," *Public Health Reviews* 34 (January 2013): 1-18.

[25] To quote a recent publication from Reverby on the Guatemala story: "When something horrific happens, it is, of course, easier to try and find who is responsible and to judge them accordingly as evil. It is simpler to tell researchers not to be [some dead guy we now all believe was an unethical doctor] than it is to remind them that they could be him. For to understand this possibility is to come to terms with the pressures to find answers for a dreadful disease [or condition], to believe that the higher calling of science makes certain ethical shortcuts possible, and that even supervisory personnel and institutional review boards do not always understand why certain studies should never be started or should be stopped." Susan M. Reverby, "Will the STI Studies in Guatemala be Remembered, and for What?" *STI* 89 (June 2013): 301-302.