Presentation for

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Protection of Human Subjects and

Research Studying Standard of Care Interventions

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by

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My presentation summarizes the main points made in an August 7 submission by me and my colleagues in the Department of Health Law, Bioethics & Human Rights at Boston University, Professors Leonard Glantz and Michael Grodin on Research on Standard of Care Interventions. As with that submission, I am speaking for myself, and not for Boston University or any other entity. I note that informed consent has been a major subject of our own research, and that two of us wrote the informed consent background papers for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1975, and together the three of us have almost 100 years of experience as being either the chair or a member of an IRB at a major medical research institution.

I will make four interrelated points: (1) There is a difference between research and treatment, (2) informed consent (including disclosure of risks and alternatives) is required for both, (3) there is nothing special about "standard of care research" and (4) randomization always deprives the research subject of the best judgment of their physician, and potential research subjects must know this.

First, there are fundamental differences between research and treatment, differences that explain why we have a prior IRB review system. To put it briefly, treatment involves decisions made in a doctor-patient relationship where the physician has a fiduciary duty to act in the best interests of the patient with the patient's consent. Research done by physicians has the purpose of generating knowledge for the benefit of other people, knowledge made generalizable by following a protocol for all subjects, rather than providing individualized treatment. A physician's actions must be guided by a fiduciary obligation to the patient. A researcher has no such obligation (although, of course, must terminate the experiment if the subject's life or health is at great risk). In the case of a randomized trial, assignment of a subject to one or another arm of the study is determined by a metaphorical flip of a

coin and not based on what a physician thinks is the best treatment, and is consistent with the patient's values and consent.

A patient has a right to a physician who is duty-bound to protect their health interests, the research subject does not. In effect, by volunteering to be a research subject the patient has waived their right to have health decisions made by their physician's best medical judgment. This can be a stressful situation, and may help explain what has been termed the "therapeutic illusion," seeing a physician-researcher as the subject's personal physician, and the research activity as treatment, and themselves as patients rather than subjects. IRBs are currently the primary procedural mechanism to help reduce the likelihood of this form of self-deception.

Second, although there is a difference between research and treatment, the doctrine of informed consent applies to both. In each case physicians and physician-researchers have legal and ethical obligations to obtain the patient's voluntary informed consent to any intervention that involves risks, including dignitary harms. What those risks include can be debated in both the therapeutic and research contexts (and often are in IRB meetings and consent form reviews). But at a minimum, the doctrine of informed consent requires the disclosure of "material risks," defined by the California Supreme Court quite rightly as any risk that could cause a reasonable person to reject the proposed medical treatment (or research project). In this context it is worth underlining that risks of death or serious or permanent bodily disability are always material risks that must be disclosed. Not having a personal physician to make medical decisions with is also a material risk that must be clearly explained to the prospective subject.

Third, there is nothing special or privileged about either the medical "standard of care" or so-called standard of care research. Standard of care is simply a term that is used to describe what doctors tend to do in certain circumstances. It is a description rather than a technical, scientific, or even medical

concept. Standards of care come from a variety of sources and serve a variety of purposes. There is no entity that creates the standard of care or that controls how physicians should exercise medical judgment to make decisions with their patients. Often derived from expert consensus panels, they are often referred to simply as "practice guidelines." But they can also come from what physicians learn at conferences, from drug companies, habits formed in residency, and other informal sources. For those who argue that doctors practice "defensive medicine," these practices are created by physicians based on their understanding (or misunderstanding) of their risks of being sued, and are created to protect physicians rather than patients. The right question is not whether a proposed intervention is standard of care in the research setting, but how it is to be accurately described to patients or research subjects, including its reasonably foreseeable risks and benefits, and the alternatives available.

Fourth, when randomization is used to assign a subject to one of two or more arms of a study, the potential risks and benefits of both arms (when there are two) must be explained, whether or not each could qualify under some circumstance as consistent with the "standard of care" for treating the condition being studied. For example, in the 1980s there was a substantial controversy regarding the comparative risks and benefits of radical and segmental mastectomy, both being used as standard of care by some physicians. To resolve the controversy a trial was conducted in which women with breast cancer were randomly selected for one treatment or the other. It is hard to imagine that anyone would seriously argue that this is low risk research because both treatments were commonly used by some physicians, or that the potential subjects would not need to be informed of the potential risks and benefits of each treatment before they consented to be randomized.

Randomization to determine treatment harms the subject by deprives the subject of the special doctor-patient fiduciary relationship in which their physician has an obligation to act in the patient's best interest. IRBs should never be allowed to waive informed consent for research involving

randomization into standard of care interventions. Secret randomization is never ethically justifiable. Failure to inform research subjects that they actually are research subjects is the epitome of disrespect for persons, and results in people being used simply as a means to other people's ends.

All of these points can be applied to the SUPPORT study which OHRP properly criticized for failure to disclose the risks of death and blindness, and their different likely tradeoffs, in the two arms of the oxygen saturation trial. Making such tradeoffs between mortality and morbidity has been a problem in the neonatal intensive care units for more than 60 years. There is no real dispute, however, that only parents should be able to make decisions about this tradeoff, whether in research or treatment.

The case of Daniel Burton provides a useful summary. Daniel was born prematurely in 1953, and shortly after his birth he was enrolled in a study, without his parents' knowledge, in which he was randomly assigned to high levels of oxygen, resulting in blindness. The Appellate Division of the Supreme Court of New York affirmed a jury verdict against the hospital and the chair of pediatrics in 1982. That opinion, *Burton v. Brooklyn Doctors Hospital*, 88 A.D.2d 217 (1982) is good law and deserves wide readership. The court found failure to obtain consent for randomization was not excused because the treatment arm to which Daniel was assigned "was in accordance with applicable 1953 community standards." The court also noted that even if the treatment Daniel got was "acceptable medical practice," using it without informed consent deprived Daniel of having a physician who "should use his best judgment and whatever superior knowledge, skill or intelligence he has" to care for the patient.

Whether standard of care research, clinical-effectiveness research, patient-centered outcomes research, or research in the context of a learning healthcare institution, IRBs must review each study based on its specific goals, outcomes, risks and benefits. This review must be conducted in an atmosphere in which the rights and welfare of research subjects take primacy over an investigator's needs, and even over the benefit the research may provide to society.

Appendix

George J. Annas

George Annas, William Fairfield Warren Distinguished Professor at Boston University, is Chair of the Department of Health Law, Bioethics & Human Rights of Boston University School of Public Health, and Professor in the Boston University School of Medicine, and School of Law. He is the cofounder of Global Lawyers and Physicians, a transnational professional association of lawyers and physicians working together to promote human rights and health. He has degrees from Harvard College (A.B. economics, '67), Harvard Law School (J.D. '70) and Harvard School of Public Health (M.P.H. '72).

Professor Annas is the author or editor of 18 books on health law and bioethics, including *Worst Case Bioethics: Death, Disaster, and Public Health* (2010), *Public Health Law* (2007), *American Bioethics*: *Crossing Human Rights and Health Law Boundaries* (2005), *The Rights of Patients* (3d ed. 2004), *Some Choice*: *Law, Medicine, and the Market* (1999**),** *Standard of Care*: *The Law of American Bioethics* (l993), and *Judging Medicine* (1987), and a play entitled *Shelley's Brain*, that has been presented to bioethics audiences across the U.S. and in Australia. Professor Annas wrote a regular feature on "law and bioethics" for the *Hastings Center Report* from 1976 to 199l, and a regular feature on "Public Health and the Law" in the *American Journal of Public Health* from 1982 to 1992 and since 1991 has written a regular feature for the *New England Journal of Medicine* ("Health Law, Ethics & Human Rights").

He is a fellow of the American Association for the Advancement of Science, a member of the Institute of Medicine, a member of the National Academies' Human Rights Committee, and co-chair of the American Bar Association's Committee on Health Rights and Bioethics (Individual Rights and Responsibilities Section). He has also held a variety of government regulatory posts, including Vice Chair of the Massachusetts Board of Registration in Medicine, Chair of the Massachusetts Health Facilities Appeals Board, and Chair of the Massachusetts Organ Transplant Task Force.

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