

Oct. 26, 2011

Jerry Menikoff, MD, JD  
Office for Human Research Protections  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852

Re: Docket No. HHS-OPHS-2011-0005

Dear Dr. Menikoff,

On behalf of the Second Wave Initiative, a consortium of physicians, scientists, and bioethicists working to advocate for the importance of advancing the evidence base for the treatment of pregnant women facing serious illness, we are pleased to provide comments on “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (Federal Register Thursday, July 26, 2011, 44512–44531; Federal Register Thursday, September 1, 2011, 54408). We congratulate the hard work and significant progress represented by the proposed changes to regulations governing human participation in research (45 CFR part 46, subpart A; “the Common Rule”).

The ANPRM suggests significant changes to 45CFR46, many of them welcome. Because this announcement has initiated a process to modernize the regulations that will not likely be undertaken again anytime soon, it is critical that the proposed changes address serious deficiencies in the current regulatory structure. We note an area of omission in the ANPRM that is of particular concern: namely, improving guidance on research with pregnant women.

Over 500,000 women in the United States face serious medical illness while pregnant, but we have a paucity of information on how to safely and effectively treat them. Researchers have been understandably skittish about this area; and the current regulations contain both vagaries and constraints that make it difficult for researchers to feel comfortable understanding the parameters of responsible research with pregnant women.

This comes at a substantial cost to the health of both women and their newborns. First, medications needed to treat significant illnesses are often metabolized by the pregnant body in very different ways than by the non-pregnant body, and evidence-based dosing of medications for pregnant women sorely lacking; second, information specific to safety in use during pregnancy is needed; finally, in the absence of the sort of reassurance that proper research can provide, the lack of evidence base can contribute to a reticence on the part of some pregnant women or their providers to use medication that is in fact critical to support the health of the woman and newborn.

Without better direction from the regulations, researchers will, we fear, continue to

sidestep the issue, leaving intact our ignorance about how to safely and effectively treat pregnant women who face serious illness.

We urge in the strongest possible terms the following:

1. Amend 45CFR46.204 (Subpart B) to add a category of “minor increase over minimal risk” or its equivalent. Currently, any research that does not carry the potential for direct health benefit to pregnant woman or fetus is disallowed unless it involves “no more than minimal risk.” In practice, this policy has led to an untoward chilling of research. The concept of minimal risk is challenging; in the context of research in pregnancy, it has been interpreted incredibly conservatively. To give just one example, we have had experience with government officials who interpret this as ruling out pharmacokinetic studies with pregnant women – an extremely low risk study methodology that is critical to determining dosing of medications in pregnant women. We strongly urge that the regulations here follow the lead taken in pediatric research (another research arena with special ethical complexities), that of adding and allowing the category of “minor increase over minimal risk” or its equivalent. In the absence of such a category, interventions with any risk will necessarily continue to be initiated, untested, in clinical contexts, thereby exposing women and fetuses to the possibility of harm without creating generalizable knowledge.

2. Amend 45CFR46.204e to remove the paternal consent requirements on research. While endorsing the good intentions behind this regulation, we note that in practice it is worrisome, for the reasons put forward by the Ethics Committee of American College of Obstetrics and Gynecology statement against the requirement for paternal consent. The claim is not that the interests of both parents in the well-being of their offspring are unimportant, but rather how this claim is instantiated in practice and research rules. We note that in pediatric research, paternal consent is required only for research in which there is no prospect of direct benefit for the child and the risks are greater than minimal; not only are the pediatric regulations less restrictive, but they also apply to research that does not involve the health of another, namely the pregnant woman.

3. Amend 45CFR46.107 and §46.111 to remove language labeling pregnant women as a vulnerable population, defined in the document as a population that is at high risk of coercion and undue influence. Pregnant women are indeed a highly complex population for consideration as research participants: there are specific scientific and ethical challenges that require specific attention. But it is misleading and unhelpful to describe these complexities as equivalent to being at risk of coercion and undue influence. Such a formulation unintentionally casts pregnancy as a condition that inherently threatens women’s ability to make rational, informed, and voluntary decisions; it also distracts from the significant and gestation-specific issues that urgently need attention. Thus, while we concur with the current proposal that for expedited studies, criteria 3 and 8 (which include pregnant women) in 46CFR46.111 should not be required for IRB approval, we strongly urge changing the language from “vulnerable” to “population meriting special regulation.”

4. Explicitly confirm that the proposed changes with regard to excused and expedited research include research with pregnant women, to avoid inappropriate exceptionalism about pregnancy on the part of researchers and institutional review boards.
  
5. Establish and formally charge a working group to propose new model language for the special regulation of clinical research with pregnant women that strikes a more appropriate and more just balance of rights, needs, and interests. Even if suggestions 1-4 proposed here are adopted, but especially if they are not, the current regulatory structure puts forward serious barriers to the conduct of research on the health needs of pregnant women and the securing of evidence-based direction on how best to treat women who face serious medical illnesses while pregnant.
  - i. Lyerly AD, Little M, Faden R. Pregnancy and Clinical Research. *Hastings Center Report* 2008;38(6):53.
  - ii. Baylis F. Pregnant Women Deserve Better. *Nature* 2010;465(7229):689-90.
  - iii. Chambers CD, Polifka JE, Friedman JM. Drug Safety in Pregnant Women and their Babies: Ignorance Not Bliss. *Clinical Pharmacology and Therapeutics* 2008;83(1):181-3.
  - iv. Second Wave Initiative at <http://secondwaveinitiative.org/>

Thank you so much for the opportunity to submit these comments, and congratulations again on the work that has been accomplished.

Sincerely,

Margaret Little, BPhil, PhD  
Director, Kennedy Institute of Ethics  
Georgetown University  
Washington, DC

Ruth Faden, PhD, MPH  
Director, Berman Bioethics Institute  
Johns Hopkins University  
Baltimore, MD

Anne Drapkin Lyerly, MA, MD  
Assoc. Director, Center for Bioethics  
University of North Carolina at Chapel Hill  
Chapel Hill, North Carolina

## CO-SIGNATORIES

Name	Affiliation	Address	Email
Katherine Wisner, MD	Director, Women's Behavioral HealthCARE	University of Pittsburgh Western Psychiatric Institute and Clinic 3811 O'Hara St Pittsburgh PA 15213	wisnkl@upmc.edu
Kelly Edwards, PhD	Assoc. Prof., Dept. of Bioethics & Humanities, University of Washington School of Medicine	Department of Bioethics and Humanities University of Washington School of Medicine Box 357120 Seattle, WA 98195	edwards@u.washington.edu
Sharon Maynard, MD	Assoc. Clinical Prof, George Washington University School of Medicine	Dept. of Medicine Lehigh Valley Health Center 1250 S. Cedar Crest Blvd Allentown, PA 18105	sharonmaynard@gmail.com
Richard Beigi, MD, MSc	University of Pittsburgh, Magee-Women's Hospital	Magee-Womens Hospital of the University of Pittsburgh Medical Center Office #2326 300 Halket Street Pittsburgh, PA 15213	rbeigi@mail.magee.edu
Patricia King, JD	Professor, Georgetown University Law School	Georgetown Law School 600 New Jersey Avenue NW Washington, DC 20001	patricia.king1@gmail.com
Anna Mastroianni, JD	Professor, University of Washington School of Law and Institute for Public Health Genetics	University of Washington School of Law & Institute for Public Health Genetics 420 William H Gates Hall Box 353020 Seattle, WA 98195	amastroi@uw.edu

Name	Affiliation	Address	Email
Debra DeBruin, PhD	Interim Co-Director, University of Minnesota Center for Bioethics	University of Minnesota Suite N504 Boynton 410 Church St SE Minneapolis, MN 55455	debru004@umn.edu
Françoise Baylis, PhD	Professor, Dalhousie University School of Medicine	Dalhousie University School of Medicine Novel Tech Ethics 1379 Seymour Street P.O. Box 15000 Halifax, Nova Scotia Canada B3H 4R2	francoisebaylis@eastlink.ca
Rebecca Kukla, PhD	Sr. Research Scholar, Kennedy Institute of Ethics, Georgetown University	415 Healy Hall, Georgetown University, Washington DC 20057	rk75@georgetown.edu
Anna Rachel Brandon, PhD, ABPP	Clinical Assistant Professor, University of North Carolina at Chapel Hill Department of Psychiatry	University of North Carolina at Chapel Hill Department of Psychiatry Women's Mood Disorders Center Campus Box 7160 Chapel Hill, NC 27599-7160	<a href="mailto:anna_brandon@med.unc.edu">anna_brandon@med.unc.edu</a>
Vanessa Merton, JD	Professor, Pace University School of Law	Pace University School of Law 78 North Broadway White Plains NY 10603	vmerton@law.pace.edu
Toby Schonfeld, PhD	Director, Masters in Bioethics, Associate Professor, Medicine, Emory University School of Medicine	Emory University 1531 Dickey Drive, 1st floor Atlanta, GA 30322	toby.schonfeld@emory.edu
Kimberly Yonkers, MD	Professor of Psychiatry and of Obstetrics, Gynecology, and Reproductive Sciences and Lecturer in Epidemiology (Chronic Diseases); Director, PMS and Perinatal Psychiatric Research Program, Yale Medical Group	Yale Psychiatry 142 Temple Street New Haven, CT 06510	kimberly.yonkers@yale.edu

Name	Affiliation	Address	Email
N. Jean Amoura, MD, MSc	Assoc. Professor, Ob-Gyn, University of Nebraska Medical Center	University of Nebraska Medical Center 983255 Nebraska Medical Center Omaha, NE 68198-3255	jamoura@unmc.edu
Kate Greenwood, JD	Research Fellow & Lecturer in Law Center for Health & Pharmaceutical Law & Policy, Seton Hall Law School	Seton Hall Law School One Newark Center Newark, NJ 07102	kate.greenwood@shu.edu
Robyn MacQuarrie, MSc, FRCS	Novel Tech Ethics Program, Dalhousie University	Novel Tech Ethics Dalhousie University 5248 Morris Street Halifax, Nova Scotia B3H 4R2	RMACQUAR@dal.ca
Gary Shangold, MD	President, InteguRx Therapeutics LLC	14 Laurel Mountain Way Califon, NJ 07830	gshangold@comcast.net
Charles McCarthy, MD	Former Director of the Office for Protection from Research Risks (OPRR), NIH		charliemc83@gmail.com
LeRoy Walters, PhD	Sr. Research Scholar, Emeritus, Kennedy Institute of Ethics, Georgetown University	7118 Exfair Road, Bethesda, MD 20814-5503	waltersl@georgetown.edu
Steven J. Ralston, MD	Tufts Medical Center	Tufts Medical Center 800 Washington St Boston, MA 02111	sjralston@tuftsmedicalcenter.org
John Sadler, John Sadler, MD	Professor of Medical Ethics, University of Texas Southwestern Medical Center	UT Southwestern 5323 Harry Hines Boulevard Dallas, TX 75390-9070 USA	<a href="mailto:John.Sadler@UTSouthwestern.edu">John.Sadler@UTSouthwestern.edu</a>

Name	Affiliation	Address	Email
Simon Lee, PhD, MPH	University of Texas Southwestern Medical Center	UT Southwestern Medical Center, Dept of Clinical Sciences MSC 9066, 5323 Harry Hines Boulevard, Dallas, Texas 75390	SimonCraddock.Lee@UTS outhwestern.edu
Ruth Macklin, PhD	Professor of Bioethics, Albert Einstein College of Medicine	Epidemiology & Population Health Albert Einstein College of Medicine 1300 Morris Park Ave. Bronx, NY 10461	<a href="mailto:ruth.macklin@einstein.yu.edu">ruth.macklin@einstein.yu.edu</a>
Joseph Biggio, Jr., MD	Director, Division of Maternal Fetal Medicine   Medical Director, Obstetric Services Associate Professor   Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Department of Obstetrics and Gynecology	University of Alabama at Birmingham, Department of Obstetrics and Gynecology 1702 6th Ave. So, Women and Infants Center STE 10270Q Birmingham, AL 35249- 7333	<a href="mailto:joseph.biggio@obgyn.uab.edu">joseph.biggio@obgyn.uab.edu</a>
Nancy Kass, ScD	Professor of Bioethics and Public Health, Johns Hopkins Berman Institute of Bioethics & Bloomberg School of Public Health	Johns Hopkins Bloomberg School of Public Health Deering Hall 1809 Ashland Avenue Baltimore, MD 21205	nkass@jhu.edu

Name	Affiliation	Address	Email
Miriam Kuppermann, PhD, MPH	PhD, MPH Professor, Obstetrics, Gynecology and Epidemiology Director, Program in Clinical Perinatal and Comparative Effectiveness Research, University of California, San Francisco	3333 California Street, Suite 335 San Francisco, California 94143-0856	<a href="mailto:kuppermannm@obgyn.ucsf.edu">kuppermannm@obgyn.ucsf.edu</a>
Tom Beauchamp, PhD	Sr. Research Scholar, Kennedy Institute of Ethics, Georgetown University	Healy Hall Georgetown University Washington DC 20057	beauchat@georgetown.edu
Hadar Sheffer, MPH		1207 W. North Loop Blvd #A Austin, TX 78756	hadarhana@gmail.com
Elizabeth Mitchell Armstrong, PhD	Associate Professor of Sociology and Public Affairs Princeton University	Office of Population Research 253 Wallace Hall Princeton, NJ 08544	ema@princeton.edu
Lisa Harris, MD, PhD	Assistant Professor Department of Obstetrics and Gynecology Department of Women's Studies Program in Sexual Rights and Reproductive Justice University of Michigan	L4000 Women's Hospital 1500 East Medical Center Drive Ann Arbor MI 48109	lharris@med.umich.edu