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,

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