This document, completed in October 2011, is in response to the US Department of Health and Human Services (HHS) "Advance notice of proposed rulemaking" (ANPRM) dated July 26, 2011 in regard to revising and updating HHS human subject research protections.

This letter proposes explicit inclusion of an additional dimension of public health-related human subjects research protection.

Our Document ID is: HHS-OPHS-2011-0005-**1070**

Document Type: Public Submission
This is "comment" on Notice: Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators
Docket ID: HHS-OPHS-2011-0005

www.regulations.gov/#!documentDetail;D=HHS-OPHS-2011-0005-1070

Document Subtype:	Public Comment
Status:	Posted
Received Date:	**October 26 2011, at 10:14 PM** Eastern Daylight Time
Date Posted:	October 27 2011, at 12:00 AM Eastern Daylight Time
Comment Start Date:	July 26 2011, at 12:00 AM Eastern Daylight Time
Comment Due Date:	October 26 2011, at 11:59 PM Eastern Daylight Time
Tracking Number:	80f5d6ce
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Our online comment field (searchable):

"**See attached file. The issue addressed is that there is a critical need to address in the Federal regulations both benefit to individuals and protection of the public. We urge that the Common Rule be amended to explicitly require certain considerations of societal effects of research, including but not limited to public health issues. We propose a mechanism for this to be taken into routine account while minimizing the burden. We provide some brief examples regarding these matters. These issues need to be routinely and consistently addressed by IRBs.**
This letter REPLACES our submission from earlier today, HHS-OPHS-2011-0005-1028.
The authors include seventeen senior epidemiologists, ethicists, geneticists and minority health experts from within and outside the US."

October 26, 2011

Jerry Menikoff, M.D., J.D.
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Re: HHS-OPHS-2011-0005: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Dear Dr. Menikoff:

The comments below pertain especially to Question 27 of the ANPRM, HHS-OPHS-2011-0005. However, rather than addressing the question of whether IRBs correctly interpret the relevant present clause in the Common Rule, we argue that the principles of **both benefit to individuals and protection of the public require** that the Common Rule be amended to explicitly require certain considerations of societal effects of research.

This letter REPLACES our submission from earlier today, HHS-OPHS-2011-0005-**1028;** it remains unchanged except for now having additional signatories. The authors include seventeen senior epidemiologists, ethicists, geneticists and minority health experts.

The Joint Policy Committees of the Societies of Epidemiology (JPC-SE), in the response to the ANPRM that has been submitted separately, made some important points, with which we concur, in responding to Question 24 by proposing language differentiating public health practice (PHP) and research.

In this letter, which we acknowledge has a philosophical bent, we wish to suggest to OHRP that **further work in this area is necessary and important**. In our joint experience, we have seen local IRBs reach different conclusions about the importance of addressing the issues below. Furthermore, there are critical issues that need to be considered — as society itself should always be considered in these contexts as one of the *de facto* subjects, and thus the regulations constructed so that society is also "protected' when appropriate.

The differentiation proposed in the JPC-SE response between PHP and research (with which we are in full agreement) serves to protect us on the side where PHP promotes the public good.[1] There are, on the other hand, instances where we would want an IRB or regulators to weigh in

[1] Obviously, exclusion of PHP from IRB review would not exclude IRB review of all activities that purport to promote the public good. Research on human subjects that is justified by its societal benefits must of course remain subject to principled review that respects the usual prohibitions against putting uninformed subjects at risk.

where a project has potential to help an individual subject but contains the possibility of harm to society or to a subgroup of society. So, this opposite side of the coin of the issue still needs to be addressed. The current regulations do not systematically force consideration of this issue[2], nor do we see the new regulations or the posed questions dealing with this.[3]

- An example of potential harm to all of society: consider a project where the therapeutic change might enhance transmissibility, infectivity, or increase microbial resistance. Obviously, a research proposal to treat everyone who has symptoms of an upper respiratory infection with an antibacterial agent would pose a serious public health threat.
- An example of potential harm to a subgroup of society: The Havasupai tribe, in Arizona, considers all material obtained from tribe members to be sacred. There is a well-known example where the elders of the tribe were not consulted regarding some secondary uses of specimens that had been obtained. A new IRB section requiring investigators to pay attention to medical, socio-cultural, and other relevant factors would help to avert such unintentional consequences by requiring such aspects to be understood by the investigators and presented to the IRB for deliberation.

Proposal: A way to deal with this is to require a NEW additional section for all projects undergoing IRB review, attesting to whether or not there are any plausible public health risks.

If not, only a single short phrase would be needed in reply; the remainder of this new, but required, section could be left blank (or a short explanation given) — thus this would not pose any meaningful new burden upon most investigators.

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[2] Indeed, they appear on the surface to explicitly prohibit such consideration, although we will argue in our further explanatory remarks below that there is implicit evidence suggesting that a broad construction of such a prohibition was not intended and is indeed not sensible even in the current regulations. 45 CFR 46.111(a)(2) states that

> (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: … (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). *The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.* …[*emphasis added*]

It appears that there is, at least potentially, a certain incoherence to this provision, because an assessment of "the importance of the knowledge that may reasonably be expected to result" from the research **must** often include an assessment of "possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy)." It makes no sense to assess the importance of knowledge of the effects of a new treatment without considering the potential long-range benefit or harm of using that treatment in the larger population.

[3] Similar ideas were presented at: SH Weiss. Role of research, and limitations Imposed by current funding and regulatory issues. Changes and greater consistency are both needed. At: "Special Symposium - Protecting Patients and Participants: Does It Matter Whether It's Research or Public Health Practice?" at the 135th American Public Health Association Annual Meeting & Exposition in Washington, DC 2007, Session 4129.0: Tuesday, November 6, 2007.

BUT if there might be such risks: then an explanation of risks and a discussion of the balancing of conflicts between the individual and the public (which includes any set of contacts of the individuals enrolled in the project, or the public at large) would need to be provided by the researchers, and then carefully considered and balanced by the IRB. In some instances, outside guidance might be needed.

Note that this revision will have to be clearly tailored to guide IRBs to have **a presumption in favor of the acquisition of new knowledge** when the only potential societal harm under consideration is that which might hypothetically arise from the increased knowledge itself resulting from the research. In such cases, the burden of proof for finding that the proposed research poses unacceptable risks should lie on the side of the claim that the knowledge could be **harmful** rather than the side of the claim that the knowledge could be **useful**. Thus, for example, research into potentially harmful side effects of a known effective treatment or diagnostic tool should not be prohibited only because knowledge of such side effects might reduce use of the procedure and hence theoretically harm those who might benefit from it. (On the other hand, the possibility of societal harm solely from the acquisition of new knowledge cannot be completely ruled out. A situation in which there might be a legitimate concern about the societal harm that could arise intrinsically from the acquisition of new knowledge arises when the new knowledge has the potential to increase many individuals' willingness to engage in risky behavior.)

Further explanatory remarks:

The example given in Question 27 of the ANPRM may hint that the existing provision in 45 CFR 46.111(a)(2) on consideration of "possible long-range effects of applying knowledge gained in the research" is already intended to be construed narrowly (in which case our proposed new revision is not nearly as much of a break from current regulations as it might appear). This example of what it might mean for an IRB to improperly (with respect to the existing 45 CFR 46.111(a)(2)) consider such effects is "to evaluate policy issues such as how groups of persons or institutions, for example, might object to conducting a study because the possible results of the study might be disagreeable to them." If such non-medical long-range policy effects as this example puts forth are all that 45 CFR 46.111(a)(2) is preventing IRBs from considering, it is hard to argue with the reasonableness of such a prohibition. Thus, the possibility that some members of a racial/ethnic group might object to studies of different relative frequencies of genetic susceptibility to certain diseases on the grounds that knowledge of such differences might foster discrimination is not an adequate reason to prohibit such research.[4] (This should

[4] That does not mean that it is not a good reason for researchers and policy-makers to be **sensitive** to those concerns. Members of a group that has a historical and/or present experience of oppression may with good reason be wary of genetic or other intrinsic biological explanations of high rates of a disease within that group when environmental, and specifically discrimination-related, explanations have not been fully explored and ruled out, precisely because of the possibility that genetic explanations can be abused by actual or would-be oppressors as evidence of the purported inferiority of the group. It is therefore incumbent on policy-makers fostering the investigation of such biological bases for differences in disease susceptibility in different groups to act to allay those fears by (1) making it clear that evidence of such biological bases is being collected in order to better prevent or treat the disease(s) in question as well as (2) not ignoring any continued relevance of environmental and social determinants of differences in disease rates. But, while these concerns are valid, they are not **IRB**-related. Empirically, people rarely refuse to participate in a study because of such concerns, despite the fact that Bioethics

not, however, preclude an IRB considering group-wide sensitivities to research when informed consent from a whole group is an issue, as in the Havasupai example.)

The acknowledgment that such narrowly circumscribed societal effects should **not** fall within the purview of IRB assessment of the impact of research on human subjects in fact highlights the legitimacy of consideration of societal effects that may directly affect the subjects. Surely any improvement or diminution in well-being for the research subjects that arises because of their membership in whatever subset of the population could benefit from policy changes resulting from such research (distinct from changes in their well-being directly resulting from their participation as research subjects) should be considered when assessing risks and benefits to the research subjects.

This illustrates the difficulty (or outright incoherence) of trying to separate individual from societal effects. Rather than ruling out all considerations of societal effects, which would potentially dangerously remove public health considerations from IRBs' independent assessment of benefits and risks of research, a more helpful approach would be to more tightly define which societal effects may legitimately be included in human subjects protection review and which (like the example in Q.27) are truly too remote from the research itself to be legitimate subjects for IRB consideration.

Considerations of possible harm to society will have to be weighed carefully, and the decisions to be reached will not always be easy. Such review will not always quash the research, even when the reality of the potential harms is recognized. So, for an example related to the previous one, legitimate concerns might be raised about research into attenuated live virus vaccines (such as the Sabin oral polio vaccine) when even the attenuated virus both is easily transmissible and could be pathogenic to, say, immunosuppressed individuals who come into contact with recipients of such vaccines. The fact, however, that such concerns must be given the serious consideration we propose does not imply that they would constitute *prima facie* grounds for rejecting such research. Rather, they would have to be balanced with the benefits to the individuals being vaccinated (and in this example with the benefits to society resulting from herd immunity as well), with due consideration for the possibility of actions that could be taken to minimize harms to vulnerable nonparticipants who could be exposed to recently vaccinated individuals.

Committees and human subjects policy-making bodies spend inordinate amounts of time discussing these theoretical concerns. This further points to the appropriateness of addressing such concerns in the arena of broad policy-making and removing it from the arena of human subjects protection review of specific research proposals. For example (and this is almost comic because of its triviality, but it illustrates the point), brachydactyly D, an entirely non-pathological autosomal dominant variant commonly known as "stub thumbs," is more common among peoples with ancestry in the Middle East (Jews and Palestinians) than among other groups. If one looks up "stub thumbs" in Internet search engines, the list of web sites that comes up will include any number of grossly anti-Semitic sites that present the increased frequency of stub thumbs among Jews as evidence of Jews' supposed inferiority. That such nonsense can and does occur is hardly a reason for prohibiting research on the genetics of brachydactyly D (which turn out to be rather interesting), and IRBs should indeed **not** consider the possibility that anti-Semites might abuse results of such research in deciding whether or not it should be conducted. There should be and are numerous other ways of dealing with anti-Semites' abuses without prohibiting investigations that yield such knowledge.

Consideration of both the benefits and risks to society is inescapable.

The possibility that such decisions might be difficult is not, however, reason for ignoring this issue.

Respectfully yours,

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