C A R E B | A C C E R

October 26, 2011

Jerry Menikoff, M.D., J.D.
Office of Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200, Rockville, MD 20852

Dear Dr. Menikoff,

RE: Canadian Association of Research Ethics Boards (CAREB)'s response to the *"Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators",*
HHS-OPHS-2011-0005

We thank OHRP for this opportunity to respond to the above-named advance notice for proposed rulemaking. CAREB's membership of over 300 individuals represents over 350 research ethics boards (REBs), the Canadian equivalent of the institutional review board (IRB), and, as such, has much experience in the ethics review process. More importantly, many of the REBs represented are from research institutions holding federal-wide assurances, and are therefore responsible for ensuring that American regulations, in addition to Canadian requirements, are upheld throughout the REB process and execution of the research.

As you know, the Canadian ethics review system for human research is guidelines-based, not legislation, as it is the United States. The *Tri-Council Policy Statement: Ethical Conduct for Research involving Humans* is now in its second edition (2010). While the new edition clarifies several areas, including governance, administration and process, it carefully navigates away from being prescriptive or overbureaucratic. This appears to be the direction the ANPRM is taking; cutting down on the paperwork while increasing participant protection.

As a foreign, not domestic body, CAREB has chosen not to comment on all of the specific details proposed in the ANPRM. Instead, we have commented on areas where, based on our collective experience, we feel that we can provide insight as to best practices. We hope that the comments provided below are of benefit to OHRP and to our American colleagues.

I. Background

1. The ANPRM describes in this section the issues with application of the Common Rule, which can be categorized into seven areas. While CAREB agrees that there are issues, it is important to point out that the systemic problem, in our opinion, is the overbureaucratization of a thoughtful process. The ethics review process as an objective evaluation of the risks and benefits of human research in all of its intricacies – vulnerability of participants, recruitment and informed consent, continuing review and monitoring, data analysis, security and dissemination of

results – remains valuable. Obstination of this process through the administrative minutae of long checklists, forms and endless regulatory requirements is the problem. So, while the issues of multiple IRB review for multi-site studies and appropriateness of review of social and behavioural research may be valid points for discussion, they are minor in comparison to the former, in terms of protecting human participants while reducing the burden, ambiguity and delay for investigators.

II. Ensuring Risk-based Protections

2. Revising rules for continuing review: CAREB agrees that the proposed changes would help eliminate some of the paperwork that has no bearing on participant protection. However, as proposed in the ANPRM, elimination of continuing review for minimal risk studies is problematic, both administratively and ethically: administratively, in terms of marking a study complete and therefore enabling institutions to properly enact retention and destruction schedules; ethically, because the level of risk reviewed through the continuing review process can be different from the original study. Research originally deemed as minimal risk may involve changes carrying increased levels of risk. Alternatively, higher risk research may have managed risks or changes carrying decreases in risk. Requiring continuing review for full board protocols but suspending such for expedited review protocols may lead to over-regulation of the former, and under-regulation of the latter. In all cases knowledge translation from researcher to IRB is essential to understanding the issues that occur "on the ground" and continuing to better the ethics review process. We therefore suggest that a study completion report should be retained as a minimum requirement recording the conclusion of the research project. We also strongly recommend that the requirement for full Board review for annual renewals and amendments be determined by the degree of incremental risk attributed to the renewal/amendment since the previous review. If risk is unchanged or reduced during this period, the requirement for full Board review should be at the discretion of the Chair. We feel that this step would significantly reduce the burden on IRBs while ensuring that the safety and welfare of the research participant is not compromised.

3. Revising the regulations regarding expedited review: There are two viewpoints on this item: agreement that a list continually updated would be useful and could be applied by Canadian REBs. Alternatively, the list could be removed altogether and minimal risk used as the criterion for expedited review. It is important to recognize that currently, expedited and exempt categories are determined by method and not research topic. This is problematic, as area of study is equally important in determining potential harms.

4. Revising the regulations regarding studies currently considered exempt: We suggest harmonizing US categories of exemption with Canadian exemption criteria. If lists are to be used, the determination of exemption should be applied by the IRB staff, not the researcher. Waiting for random retrospective audits will potentially allow non-exempt research to be conducted without ethics approval, which is highly problematic, no matter the risk level.

5. Written consent for use of any biospecimens: Many Canadian REBs require that use of tissues be specific to the study or disease state; open-ended use is not allowed unless samples are anonymized or patient gives future consent, as the uses are so broad that umbrella consent would be meaningless. While having open-ended written consent would simplify matters, one questions whether this would be ethically acceptable.

   Also important to note is the requirements for consent when conducting research with Aboriginal peoples. In Canada, community consultation and consent is required, in addition to individual consent. As well, it is common for certain communities to not allow open-ended use of their biospecimens, which complicates matters.

6. Mandatory standards for data security: If the IRB no longer has responsibility for assessing privacy according to HIPAA standards, which body/position then becomes responsible? May this secondary body actually increase administrative burden, instead of reducing it?

7. Full convened IRB review: as discussed above, removing the requirement for annual renewals would be helpful in reducing administrative burden. However, a study completion report should be submitted at the end of the research study.

8. Revised approach to expedited review: See point #3 above.

9. Moving away from concept of exempt: These studies are exempt from IRB review, not the regulations. The term "excused" appears to trivialize the issue.

10. Types of research studies that qualify: Research that contains potential informational harms still needs oversight by the IRB, as impact of those harms are ethical in nature, not regulatory. Furthermore, as expressed in point #6, there is no explanation as to who would then be responsible for informational harms. It is unlikely that any non-IRB committee would understand the complexity of those harms, and having an additional committee would increase the administrative burden of the review system.

11. Proposed auditing requirement: This additional process would not be helpful. Instead, OHRP should keep current practice and instead focus on educating IRBs on how to be flexible.

12. Data originally collected for research purposes: While CAREB strongly agrees with the principle of consent for secondary use of research data or biospecimens, we question how consent would be administered/ verified for anonymized data/samples. Maintaining consent forms with the data/samples would increase the risk of identification, especially if two-tiered consents were used (consent for specific types of research, and consent for all research). Perhaps it is better to maintain ethics review and no (proof of) written consent rather than written consent and no ethics review when applied to anonymized data or biospecimens.

13. Without adding significant protection: Investigators are left on their own with no oversight, except for a possible audit process in the future. Providing a

registration form to the institution, without any administrative review leaves the IRB office, institution and investigator unprepared if something goes wrong.

14. Question 14: Expansion of the "excused" category, combined with the logistics as to how the system will work diminishes attention to ethical principles and puts participants at risk. Removing the IRB from the process will weaken oversight to the detriment of participants. We therefore recommend an administrative review process for all exempt ("excused") research, which would look at: 1. Whether the research fits within the criteria; 2. Determines the informational harms; 3. Evaluates other research risks. The administrative review, which would take place within the IRB office by one staff member, would conclude through the issuing of an acknowledgement. If the study didn't fit into exempt criteria, the investigator would be told to submit for IRB review. If informational harms or research risks did exist, these could be communicated to the investigator, but would not need to come back with responses or revisions. Such a review would protect participants, investigators and the institution. Investigators would need to wait until they received their acknowledgement.

15. Question 24: Quality assurance/quality improvement, program evaluation and some public health research should be excluded if they can be adequately defined.

16. Question 27: If this is how IRBs are interpretting this regulation, it should be struck. It is essential for that feedback loop, as understanding the ethical issues "on the ground" enables them to do a better job in the furture.

17. Question 28: There should be an appeals mechanism for investigators. The Tri-Council Policy Statement (2010) has an outline for creating an appeals mechanism. This should be consulted in development of a policy.

18. Question 29: These situations are the responsibility of the IRB office, not the IRB itself. IRB administrative professionals can handle them competently.

III. Streamlining IRB Review of Multi-site Studies

19. Question 30: The only potential advantage would be speed.

20. Question 31: There is little evidence to support the notion that local ethics review adds protection to human participants in multi-site research, assuming that the central review board is competent. As the US has an accreditation system for IRBs, one supposes that those that are accredited are competent.

21. Question 32: Local boards are very concerned with regulatory and legal liability concerns. Many also suffer from "we do it better" syndrome.

22. Question 33: Local ethics review creates tremendous inefficiencies for multi-site reviews, which costs industry considerable time and money.

23. Question 34: The IRB with either: a) the most expertise in the study area, or b) the largest patient population could be the board of record. This would require negotiation and discussion by all the local sites. In many circumstances sites do not talk to one another, so such communication would be an improvement. Requiring disclosure of previous IRB decisions on the given study, coupled with discussions among IRBs would be essential to preventing IRB shopping.

24. Improving consent forms: We suggest that a checklist or a list of criteria – required, population or method–specific, and optional – be used instead of standardized consent form templates.

25. Question 38: This should be mandatory in any consent process.

26. Question 47: Consent should be sought whenever possible.

27. Question 48: Only in situations where it is impracticable to obtain consent or could be detrimental to the participant. Ethics review is required to determine these.

28. Question 50: Categories should be determined by the investigator and approved by the IRB. In general, there should only be 3 categories of consent: a)for the current study; b) for research related to the topic under investigation; c)all research. Whether categories b and c can be understood by participants (and all potential information harms associated with research that has not yet been determined) is something for ethicists, lawyers and policy-makers to decide. Another way to handle this would be to have consent for re-contact for participation in further research.

29. Question 51: The highest standard should be applied.

30. Question 52: Existing biospecimens and data sets should be grandfathered in. This will create better buy-in from investigators.

31. Question 53: This is for the IRB to decide.

Overall CAREB would like to commend OHRP for recognizing that change is needed. We have to provided you with our thoughts on the overall document, but from our perspective strongly urge you to focus on those aspects of the ANPRM that we feel are most important: proportionate review, determined principally by appropriate designation of risk; lowering of the threshhold for full Board review; the need for institutional buy-in if informational harms are to be removed from the IRB agenda; facilitation of secondary uses of information and access to tissues, (important in a rapidly changing scientific world) while ensuring that the welfare of the participant remains secure; support for the principal of centralization of ethics review for multicenter trials; shortening and simplification of the consent form driven by participant protections and advancement of science and not by the legal concerns of the sponsor.

On behalf of CAREB, we would like to thank you, once again, for giving us the opportunity to respond. We hope that our comments will be useful to further revisions of the US regulations.

Sincerely yours,

Sharon Freitag
Co-President
CAREB