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Dear Drs. Menikoff and Borror:

Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) immediately launch a compliance oversight investigation into the human subjects protection program at the University of Minnesota (UM) under Federalwide Assurance #00000312. A recently released report — commissioned by UM through a contract with the Association for the Accreditation of Human Research Protection Programs and prepared by an external review team comprising six experts[1] — appears to reveal serious, systemic failures in UM's system for protecting human subjects and widespread violations of Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 C.F.R. Part 46).

Among the most troubling findings of the external review team, discussed in greater detail below, are the following:

- The UM medical institutional review board (IRB) appears to lack appropriate expertise among its members for the research that it reviews.

[1] Association for the Accreditation of Human Research Protection Programs. An External Review of the Protection of Human Research Participants at the University of Minnesota with Special Attention to Research with Adults Who May Lack Decision-Making Capacity: Final Report. February 23, 2015. https://www.scribd.com/doc/257152188/AAHRPP-Final-Report-With-Prefatory-Note-and-Cover-Letter. Accessed March 9, 2015.

- When reviewing and approving research, the UM medical IRB appears to fail to ensure that:
  - risks to subjects are minimized and reasonable in relation to potential benefits; and
  - the informed consent of subjects always is obtained under circumstances that minimize the possibility of coercion or undue influence.

The alarming findings by the external review team echo some of the most serious instances of systemic failures of human subjects protections at major academic institutions uncovered by OHRP over the past two decades. These findings, if confirmed by OHRP, would represent a clear danger to the rights and welfare of human subjects enrolled in medical research studies at UM and, therefore, would warrant suspension or restriction of UM's Federalwide Assurance pending implementation of appropriate corrective actions, including re-review of ongoing human subjects research projects overseen by the UM medical IRB in a manner that fully complies with all requirements of 45 C.F.R. Part 46.

Key findings by the external review team requiring investigation by OHRP

(1) HHS regulations at 45 C.F.R. 46.107(a) require, among others things, the following:

> The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

OHRP for many years has interpreted the above regulatory provisions as requiring that the convened IRB, when reviewing protocol applications, must have sufficient expertise among the members **present** at the meeting to make the determinations required for approval of research under HHS regulations at 45 C.F.R. 46.111.[2]

Furthermore, HHS regulations at 45 C.F.R. 46.107(f) state that:

> An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB.

[2] Office for Human Research Protections. OHRP compliance oversight activities: Determinations of noncompliance. February 4, 2009. http://www.hhs.gov/ohrp/compliance/findings/findings.pdf. Accessed March 9, 2014. See section A(5).

The external review team report documented that from October 1, 2013, through September 30, 2014, the UM medical IRB routinely reviewed research protocols originating from the following medical school departments or divisions: adult hematology, oncology, and transplant (145 protocols); psychiatry (85 protocols); cardiology (60 protocols); surgery (46 protocols); pediatric blood/marrow transplant (45 protocols); pediatric hematology (44 protocols); pediatric endocrine (34 protocols); and neurology (31 protocols).[3] However, the external review team found the following regarding the expertise among the members of the UM medical IRB:[4]

> **[T]here were no individuals on the IRB during this time period with expertise in adult hematology, oncology and transplant, cardiology, surgery, or neurology, although those fields taken together represented over 300 protocols** [emphasis added]. There was only one psychiatrist on the IRB, despite the fact that the Psychiatry Department submitted 85 protocols for review during the time period examined.
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> Based on IRB minutes from January through July 2014, the psychiatrist on the IRB roster attended only four of 26 Medical IRB meetings at which new protocols were reviewed. **Thus, at 22 of the 26 meetings at which new IRB protocols were reviewed, there was no member present with an expertise in psychiatry** [emphasis added]. …
>
> When an IRB lacks a member with relevant expertise in a given area, federal regulations permit it to "invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB." Despite the many situations in which psychiatry protocols were reviewed without a psychiatrist present, no other expert was called upon to provide supplemental review. Instead, **the external review team was told that experts were rarely brought in for consultations** [emphasis added]. …
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> **3.2.1.3 Conclusions**
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> The IRB is, by its very charge, at the core of an HRPP [human research protection program]. Its importance as the independent body charged with ensuring that any research it approves is both ethically and scientifically sound cannot be underestimated.
>
> **This makes it all the more concerning that the Medical IRB does not routinely have the requisite number of members or expertise at its meetings**

[3] Association for the Accreditation of Human Research Protection Programs. An External Review of the Protection of Human Research Participants at the University of Minnesota with Special Attention to Research with Adults Who May Lack Decision-Making Capacity: Final Report. February 23, 2015. https://www.scribd.com/doc/257152188/AAHRPP-Final-Report-With-Prefatory-Note-and-Cover-Letter. Accessed March 9, 2015. PDF page 30.

[4] *Ibid*. PDF pages 30-32.

> **to properly handle the number of studies it reviews** [emphasis added]. Specifically, as described above, based on its review of several sets of meeting minutes and associated protocols, it was clear to the external review team that the membership of **the Medical IRBs did not include sufficient members with the scientific expertise necessary to adequately address the research being reviewed at corresponding meetings** [emphasis added]. This departure not only contravenes the University's own policy of having at least one member with "primary professional expertise in a scientific field relevant to the type of research reviewed by that panel," **but also prompts concern about the quality of review** [emphasis added]. Members who have expertise in the fields from which the protocols are drawn are uniquely suited to raise questions about study design, risks, inclusion criteria, etc. They can also educate the other members of the IRB on clinical and scientific aspects of the protocol so that other members' votes are informed. In light of the deficiencies discussed in the scientific review process as noted in Section 3 (c) (ii) of this report, the lack of sufficient expertise to fulfill this role is more concerning. …
>
> **The failure to have either adequate number of IRB members, or adequate expertise, during IRB deliberations raises profound questions about the IRB's ability to conduct a robust and reliable protocol review** [emphasis added].

The external review team provided the following summary finding regarding this issue:

> [I]n examining IRB processes **from 2011-2014, the external review team found evidence of weak and often inadequately expert review of research** [emphasis added]. The team believes this leaves… [UM's] research subjects potentially susceptible to risks that otherwise would be avoidable.[5]

The findings by the external review team strongly suggest that the UM medical IRB for at least the one-year period from October 1, 2013, through September 30, 2014, routinely failed to satisfy the IRB membership requirements of HHS regulations 45 C.F.R. 46.107(a). As a result, the IRB appears to have lacked the requisite expertise necessary to make the findings required under HHS regulations at 45 C.F.R. 46.111 when conducting initial and continuing review of research and when approving research.

(2) HHS regulations at 45 C.F.R. 46.111(a) stipulate that in order to approve research covered by the regulations, the IRB must determine that, among other things, the following requirements are satisfied:

(a) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

[5] *Ibid*. PDF page 9.

(b) 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.

The assessment of the risks and potential benefits of research is one of the most important duties of an IRB under the HHS regulations. As already discussed in key finding (1) above, the UM medical IRB appears to have routinely lacked sufficient expertise among its members to make the determinations required for approval of research under HHS regulations at 45 C.F.R. 46.111 when it convened meetings to review research.

The external review team made the following additional troubling observations and findings regarding the UM medical IRB's assessment of the risks and potential benefits of research:

> In the majority of the minutes from meetings at which new biomedical research proposals were reviewed, **the team found little discussion of the risks and benefits to subjects** [emphasis added]. … Without adequate documentation indicating that such important background information was, in fact, discussed, the external review team was not able to ascertain whether or not a thorough and meaningful discussion about the protocol's risks and benefits took place. **Without such documentation, and since supplemental information (e.g., on site interviews) did not contradict the impression that the discussion on many protocols was scant, it is unclear whether an adequate review had occurred** [emphasis added]. …[6]
>
> In addition, **the length of time allotted for IRB review was alarmingly inadequate given the number of complex items scheduled for review** on many of the IRB agendas reviewed [emphasis added].[7] …
>
> **3.2.2.3. Conclusions**
> The review process, as documented in the minutes, **does not reflect a meaningful discussion of the risks and benefits of research protocols and the necessary steps taken to protect human subjects in the face of scientific or ethical concerns** [emphasis added].[8] …
>
> Thus, the inadequate documentation of review and the sheer volume of research being reviewed, combined with the membership issue described in section 3.2.1., **suggest that the IRB review process may be unacceptable, and that it often contravenes the IRB's own policies and procedures** [emphasis added].[9] …

[6] *Ibid*. PDF page 33.
[7] *Ibid*. PDF page 34.
[8] *Ibid*. PDF page 35.
[9] *Ibid*. PDF page 35.

> **3.3.2.4.2. Conclusions**
> The review process, as documented in the minutes, **does not reflect a meaningful discussion of the risks and benefits of research protocols and the necessary steps taken to protect human subjects in the face of scientific or ethical concerns** [emphasis added]. It appears that, although the University's medical IRBs purport to rely on scientific review at the departmental level, there is inadequate evidence to suggest that the scientific reviews provide sufficient detail to inform the IRB's assessment of a protocol. Instead, the team found, at least based on the evidence it reviewed, that a portion of departmental scientific reviews lacked sufficient substance to be relied upon by the IRB. While the HRPP policies seem to recognize the importance of scientific review, there is little evidence that departmental level scientific reviews are incorporated into or used to inform IRB decision-making.[10]

The findings by the external review team strongly suggest that the UM medical IRB routinely has failed to ensure that the criteria for approval of research under HHS regulations at 45 C.F.R. 46.111(a), particularly with respect to those regarding the risks and potential benefits of research, are satisfied when conducting both initial and continuing review of research.

(3) HHS regulations at 45 C.F.R. 46.111(a)(4) and 46.116 require that in order to approve research covered by the regulations, the IRB must determine that the following requirement, among others, is satisfied:

> The investigator will seek informed consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

Furthermore, HHS regulations at 45 C.F.R. 46.111(b) stipulate that in order to approve research covered by the regulations, the IRB must determine that the following requirement is satisfied:

> When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

The external review team made several observations and findings that raise serious concerns about the apparent failure of the UM medical IRB to ensure that these requirements were being satisfied, particularly with respect to studies involving patients with psychiatric disorders that could impair decision-making capacity:

[10] *Ibid*. PDF pages 53-54.

> [T]he team's examination of research proposals and IRB deliberations at the University revealed **inadequate and inconsistent attention to the process of consent, capacity to consent, the use of surrogate decision-makers, and general efforts to address vulnerability of potential research subjects to coercion and undue influence** [emphasis added].[11] …
>
> The majority of protocols examined by the team predated the above-referenced [September] 2014 consent policy revisions. **These earlier protocols contained little or no information about the consent process and virtually no details as to how capacity would be assessed, regardless of whether a targeted population was likely to include prospective subjects with impaired decision-making capacity and regardless of the level of risk** [emphasis added]. The corresponding IRB meeting minutes similarly failed to reflect a review of these issues by the IRB.[12] …
>
> Opportunities for stronger processes for protecting potentially vulnerable subjects are broadly available in the wider research community and were, as described above, observed by the external review team in some protocols. However, studies examined by the team seldom showed the IRB to be engaged in a substantive discussion of the potential tools that might be utilized in an assessment of consent capacity.[13] …
>
> Neither University policies nor practice distinguish between vulnerability to coercion or undue influence when it could occur with subjects who are limited in their understanding of the research. This area of concern is heightened in psychiatric setting situations where there is a prospect of civil commitment (i.e., involuntary hospitalization), since that threat can increase a prospective subject's vulnerability to coercion or undue influence.[14] …
>
> **The above problem, i.e., the risk of coercion or the appearance of coercion, is further exacerbated when the principal investigator is also the treating physician and thus has the power to initiate the individual's involuntary confinement. We found only a single instance where consideration of the dual and potentially conflicting role of treating psychiatrist/investigator was addressed** [emphasis added].[15] …
>
> **3.4.2.3. Conclusions**
> While recent policy changes -- and their application -- lay important groundwork for improvements in research involving subjects who may be vulnerable to undue influence or coercion, **they do not mitigate the need for an explicit policy**

[11] *Ibid*. PDF page 9.
[12] *Ibid*. PDF page 67.
[13] *Ibid*. PDF page 70.
[14] *Ibid*. PDF page 71.
[15] *Ibid*. PDF page 72.

> **requiring the IRB to assess and impose the need for safeguards in studies where individuals subject to the threat of involuntary confinement are considered or approached for enrollment** [emphasis added]. The University should directly and thoughtfully addresses the specific issues related to the context in which acutely ill psychiatric patients are identified, recruited, and asked to consent to research. Policies are needed that reflect the imperative to refrain from seeking consent when there is situational impairment as a result of an acute physical or psychological event.[16]

(4) HHS regulations at 45 C.F.R. 46.102(c) define "legally authorized representative" as follows:

> An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Regarding UM's implementation of this definition, the external review team concluded the following:

> **3.4.4.2. Conclusions**
> The University's interpretation of the regulatory term "applicable law," and therefore **its policies defining who may serve as a legally authorized representative in federally funded research, do not appear to adequately conform to federal regulations and related guidance** [emphasis added].[17]

The conclusion of the external review team appears to indicate that the UM has allowed individuals who are not legally authorized representatives of prospective subjects under applicable law to consent on behalf of those prospective subjects to research, in violation of the requirements of HHS regulations at 45 CFR 46.116, which stipulates that no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

(5) HHS regulations at 45 C.F.R. 46.107(e) state the following:

> No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

OHRP for many years has advised that an IRB member may not be counted toward quorum when the IRB reviews research for which that member has a conflicting

[16] *Ibid*. PDF page 73.
[17] *Ibid*. PDF page 76.

interest.[18] In such cases, if the exclusion of the conflicted member results in a loss of quorum, the IRB may no longer review and approve research.

However, the external review team noted the following regarding the UM medical IRB's review of certain psychiatry research protocols:

> Further, while in attendance at these [IRB] meetings, the psychiatrist recused himself from reviewing four new protocols or changes in protocols in order to avoid a potential conflict of interest (COI) or the appearance of a conflict. **The recusal in these situations left the IRB without expertise in psychiatry, and in three of the four recusals an IRB staff member was required to join the meeting in order to maintain a quorum** [emphasis added].[19]

The observations of the external review team appear to indicate that the UM medical IRB on multiple occasions over a one-year period allowed an IRB member with conflicts of interest in research protocols being reviewed to participate in the IRB review of those protocols.

(6) HHS regulations at 45 C.F.R. 46.115(a)(2) require that, among other things, minutes of IRB meetings include written summaries of controverted issues and their resolution.

The external review team made the following observations regarding the UM medical IRB's implementation of this requirement:

> Another area of concern encountered by the team related to "controverted issues." A controverted issue usually means that there are questions, or at times disagreements, requiring a more extended discussion about a given protocol. Examples of controverted issues include concerns about placebos, payment to subjects, recruitment methods, risks, etc. In each set of minutes received by the team there is a section titled "Discussion of Controverted Issues Summary." **Most of the minutes reviewed, however, stated that "there were no controverted issues," even on those occasions when the required changes would seem to have warranted a more substantive discussion and where the IRB correspondence to the study teams indicated that "controverted issues" *had* in fact been discussed. Accordingly, the minutes did not completely or accurately appear to represent what occurred during the IRB meetings** [bolded emphasis added].[20]

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[18] Office for Human Research Protections. Training video: IRB membership. https://www.youtube.com/watch?v=GHtIbdLkSwU&p=5965CB14C2506914. Accessed March 9, 2015. See 9:27 to 9:57.

[19] Association for the Accreditation of Human Research Protection Programs. An External Review of the Protection of Human Research Participants at the University of Minnesota with Special Attention to Research with Adults Who May Lack Decision-Making Capacity: Final Report. February 23, 2015. https://www.scribd.com/doc/257152188/AAHRPP-Final-Report-With-Prefatory-Note-and-Cover-Letter. Accessed March 9, 2015. PDF page 30.

[20] *Ibid*. PDF pages 33-34.

> The findings of the external review team appear to indicate that the UM medical IRB has failed to ensure that the minutes of IRB meetings include written summaries of all controverted issues and their resolution.

Conclusions and requested action

In summary, the recently released report from the external review team appears to reveal serious, systemic failures in UM's system for protecting human subjects and widespread violations of the HHS regulations for the protection of human subjects. Given the volume of medical research conducted by UM and the seriousness of the problems identified by the external review team, it is imperative that OHRP move swiftly to investigate this matter and to take appropriate action to ensure that the large number of human subjects enrolled in medical research at UM are adequately protected.

Please note that the OHRP may share our complaint letter, with identifiers, with anyone. Public Citizen will be posting a copy on its website as well.

Thank you for your prompt attention to this urgent matter regarding the protection of human subjects. Please contact me if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

cc: The Honorable Sylvia Mathews Burwell, Secretary of Health and Human Services
Eric W. Kaler, Ph.D., President, University of Minnesota