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July 5, 2018

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Doug Bannerman, Ph.D.
Executive Director
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Department of Veterans Affairs
810 Vermont Avenue NW
Washington, DC 20420

Re: **Project Title: Myocardial Ischemia and Transfusion (MINT) Trial**
Sponsor: National Heart, Lung, and Blood Institute, National Institutes of Health (NIH)
Grant Numbers: 1U01HL 133817-01 (Principal Investigator: Jeffrey L. Carson, M.D., Rutgers Robert Wood Johnson Medical School, Clinical Coordinating Center); 1 U01 HL 132853-01 (Principal Investigator: Maria M. Brooks, Ph.D., University of Pittsburgh, Data Coordinating Center)
ClinicalTrials.gov Identifier: NCT02981407

Dear Ms. Buchanan and Dr. Bannerman:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, has received your June 7, 2018, letter describing substantive changes that were made to both the research protocol and the sample consent form for the MINT trial in response to our August 1, 2017, complaint letter about the trial to the Office for Human Research Protections (OHRP) and the Department of Veterans Affairs' (VA's) Office of Research Oversight (ORO). Although we were pleased to learn that our letter prompted these changes, we are concerned that the actions described by the OHRP and the ORO are still seriously insufficient for ensuring the protection of human subjects.

As you know, our prior letter detailed concerns that the MINT trial design, as described in the trial protocol, and sample consent form both failed to materially comply with key requirements of Department of Health and Human Services (HHS) and VA regulations for the protection of

human subjects at 45 C.F.R. Part 46 and 38 C.F.R. Part 16,[1] respectively, and failed to satisfy the basic ethical principles upon which those regulations are founded.

The MINT trial will involve randomly assigning 3,500 hospitalized adult patients with acute myocardial infarctions (heart attacks) and significant anemia to receive either a restrictive or a liberal red blood cell transfusion strategy. The primary outcome measure of the trial is the composite of all-cause mortality or recurrent nonfatal myocardial infarction within 30 days of randomization. Of note, enrollment in the trial began before our 2017 complaint letter was submitted to your offices.

Our major concerns included the following:

(1) The trial protocol failed to provide key information – including a description of current usual care blood transfusion practices for patients who have had heart attacks and are hospitalized at the institutions that are to enroll subjects – that an institutional review board (IRB) would need to make the following determinations, which are required for approval of human subjects research under HHS regulations at 45 C.F.R. § 46.111(a):

   (a) The risks to the subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk (45 C.F.R. § 46.111(a)(1)).

   (b) The risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result (45 C.F.R. § 46.111(a)(2)).

   (c) The information that is being provided to subjects when their consent is sought includes an adequate description of the trial's purpose, research procedures (including the identification of any procedures that are experimental), and reasonably foreseeable risks (45 C.F.R. §§ 46.111(a)(4) and 46.116(a)(1) and (2)).

(2) The IRB-approved sample consent form failed to provide an adequate description of the the purpose, reasonably foreseeable risks, and experimental procedures of the MINT trial, as required by HHS regulations for the protection of human subjects at 45 C.F.R. § 116(a)(1) and (2).

According your June 7, 2018, letter, after receiving our August 2017 letter, OHRP and ORO staff spoke with personnel at the NIH about the MINT trial. As a result, the protocol and consent form for the trial underwent a number of substantive changes that were reviewed and approved by all IRBs responsible for overseeing the MINT trial, including:

(1) Revising the protocol to better describe current usual care for transfusing patients having acute heart attacks;

[1] For the sake of conciseness, only HHS regulatory citations are cited hereafter.

(2) Deleting from the protocol a statement that mischaracterized the risks of the research. In particular, your letter noted the following:

> In addition, the protocol has a section entitled 'Ethical Considerations' that initially included the following: 'Both transfusion strategies assessed in this trial are widely used in clinical practice. There is uncertainty about which strategy is better, and therefore there is clinical equipoise to conduct this study. Thus, there are no clinical risks to patients above those of usual practice.' It is OHRP's and ORO's view that this characterization of the risks associated with the MINT trial was incorrect. Following discussions with the NIH, the statement that 'there are no clinical risks to patients above those of usual practice' was removed from the protocol.

(3) Adding to the trial protocol a new requirement that a potential subject may not be enrolled unless the person's attending physician, with expertise in cardiovascular care, believes that both of the transfusion strategies are consistent with good medical care for the subject as determined by the physician's clinical judgment; and

(4) Revising the consent form to include a more appropriate description of the purpose of the research and a description of the possible risks of the restrictive transfusion strategy. In particular, the original consent form stated the following regarding the risks:

> **What are the risks and/or discomforts you might experience if you take part in this study?**
>
> Some blood transfusions cause problems. These bad effects of blood do not happen often and most of the time get better with treatment. The most common of these rare side effects is high temperature, chills, and allergic reactions. More rarely blood can transmit viral infections such as hepatitis (liver infection) or lead to extra fluid in the lungs. The important risks of blood transfusion are also described in the consent form that the hospital will have you sign before receiving a transfusion.
>
> There may be risks and discomforts resulting from having blood transfusions or from having transfusion delayed that are not yet known.

According to your letter, the risk section of the consent form has been revised substantively such that it now read as follows:

> There are potential risks associated with each of the blood use plans. In patients with heart attacks it is unknown whether one of the plans is safer than the other. Nearly all studies in patients with other medical problems with low red blood cell counts have shown that the risk of death and other complications does not change significantly if they receive more or fewer blood transfusions. There are a few studies that suggest giving fewer blood transfusions to patients with heart problems may increase the risk of having a second heart attack or dying. However, doctors are not sure that this is correct because there are other studies that do not show an increase risk of death or heart attacks with less transfusion and the studies were too small and included too few patients with heart attacks.

> The people in this study who are assigned to get blood only if their red blood cell count is less than 8 are likely to get fewer blood transfusions than the patients in the other group. Some doctors think that giving fewer blood transfusions and allowing a patient's red blood cell count to be lower increases the risk of complications such as more heart damage or another heart attack. On the other hand, the people who are assigned to get blood if their red blood cell count is less than 10 are likely to get more blood transfusions than the patients in the other group which may lead to higher risk for shortness of breath and fluid overload. Blood transfusions may sometimes cause other problems. These bad effects of blood do not happen often and most of the time get better with treatment.
>
> The use of blood or blood products has the following general risks: Uncommon (1-5%) chance) risks include mild reactions resulting in itching, rash, fever, headaches. Rare risks (<1% chance) include: respiratory distress (shortness of breath, tluid overload) or lung injury; exposure to blood borne micro-organisms (bacteria and parasites) that could result in an infection; possible effects on the immune system, which may decrease the body's ability to fight infection; or shock (low blood pressure). Risks that are extremely rare (approximately one in a million or less) include; exposure to blood borne viruses such as hepatitis C or Hepatitis B (inflammatory diseases affecting the liver); Human Immunodeficiency Virus (HIV, the virus that causes AIDS); death.
>
> There may be risks from not receiving blood or having transfusion delayed or risks from transfusions that are not yet known. At this point, there is not enough information to know if transfusing patients with heart disease at a higher or lower red blood cell count will increase, decrease or have no impact on their health. This is why a study such as MINT is needed.

Conclusions and requested actions

In your letter, you stated that "OHRP and ORO believe that the protocol and consent revisions made by the study team and accepted by the National Heart, Lung and Blood Institute (NHLBI) appropriately address important concerns raised about the MINT trial." You concluded that "[b]ased on the information we have about the MINT study, it is our opinion that with these revisions, the study complies with the requirements of the HHS and VA regulations for the protection of human subjects at 45 CFR Part 46 and 38 CFR Part 16, respectively."

Given the OHRP's and ORO's stated conclusions, we can only infer that the OHRP and ORO determined that the MINT trial protocol and sample consent form originally approved by the IRBs failed to materially comply with key provisions of the HHS and VA regulations for the protection of human subjects. These circumstances represent serious noncompliance when the IRBs initially reviewed and approved the trial. Moreover, any subjects enrolled using the seriously deficient original IRB-approved sample consent form were deprived of key information regarding the purpose and risks of the research and, thus, their legally effective ***informed*** consent clearly was not obtained prior to their involvement in the research.

Such serious noncompliance with key provisions of the federal regulations demands further corrective actions to ensure that human subjects are adequately protected. We therefore urge the OHRP and ORO to take the following additional actions:

(1) Require that the institutions for the IRBs that reviewed and approved the original MINT trial protocol and sample consent form develop and implement written plans for ensuring that the reviews of future clinical trials by their IRBs comply with all requirements of federal human subjects protection regulations. In particular, the plans should include provisions for ensuring that IRBs understand how proposed clinical trial interventions relate to usual clinical care before approving research.

(2) Require that the MINT trial investigators develop and implement, with IRB oversight, a plan for immediately contacting all subjects (or surviving family members of subjects) who were enrolled in the MINT trial using the original seriously deficient sample consent form and provide those subjects with accurate information about the purpose and risks of the research.

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

Sincerely,

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

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
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Enclosures

cc: Jerry Menikoff, M.D., J.D., Director, Office for Human Research Protections